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ORIGINAL ARTICLES

RUBBER TUBING AS A FACTOR IN REACTION TO THE BLOOD TRANSFUSION

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IN an article in the *Journal of the American Medical Association,* April 10, 1920, Dr. John H. Stokes and I described reactions of patients receiving intravenous injections of arsphenamine and alkaline solutions through a certain brand of rubber tubing. These reactions were characterized by chills, with a sharp rise in temperature coming on from thirty minutes to one hour after intravenous injection, and nausea, vomiting, diarrhea, pain in the head and back, and varying degrees of prostration. The reactions appeared in crops, so to speak, and then disappeared for a time, only to recur in the very midst of what seemed a period of flawless technical accuracy.

The results of a preliminary study of the possible causes of such reactions led us to the following conclusions:

1. A certain widely distributed brand of so-called pure gum rubber tubing seems to contain, when new, a toxic agent responsible for a definite type of reaction following the intravenous administration of arsphenamine, and possibly alkaline solutions and transfusion mediums.

2. The toxic substance gradually disappears from the tubing on use.

3. A pure gum rubber tubing can be made which does not produce reactions even when new.

4. The toxic substance is apparently removable in the first instance by soaking the tubing for six hours in normal sodium hydroxide solution and rinsing.

5. The toxic substance is not destroyed in the ordinary process of sterilization by boiling for from one-half to one hour; is not soluble in water or removable by irrigation; appears in toxic amounts in arsphenamine, neoarsphenamine, and dilute sodium hydroxide solution merely by passing them through a new tube 80 cm. long, enroute from container to vein, and is not apparently associated with the mechanically removable debris from the inner surface of the tube.

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6. The reaction can be induced in typical form in dogs.

That a certain number of persons have been observed to experience a somewhat similar reaction following blood transfusion by the citrate method led me to study the possible relation of this reaction to new rubber tubing. The transfusion reaction in question, although not so severe as that following the intra-

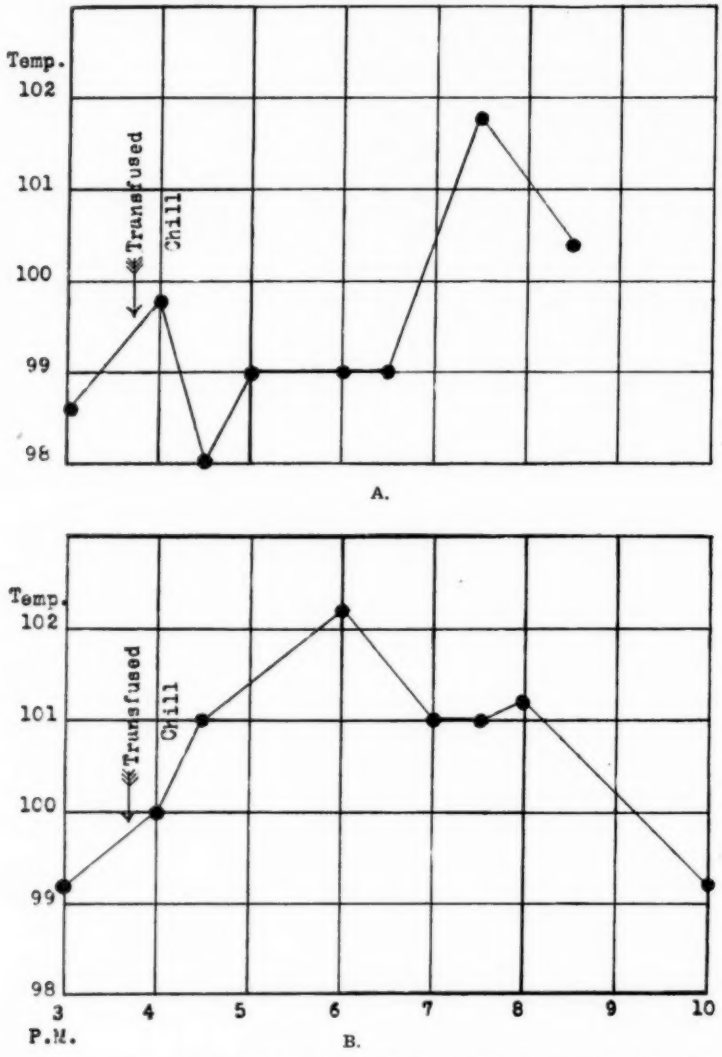

Chart 1.—Tubing reaction in man following transfusion by the citrate method in which new tubing had been used. Note that both patients developed a chill about one half hour after transfusion, followed by rise in temperature.

venous administration of arsphenamine through new tubing, consists of a chill coming on from one half to one hour after injection, a gradual rise in temperature (Chart 1), varying grades of prostration, and occasionally nausea and vomiting.

Considering the fact that the toxic substance is present in sufficient amounts to produce reactions in patients receiving the first ten to twenty-five injections of arsphenamine given through a new tube, 80 cm. in length, it is conceivable that

if the toxic substance is soluble in blood or transfusion mediums a number of patients receiving blood transfusion through a new tube would show reaction. Since this number of transfusions in most clinics or hospitals would extend over a relatively long period, the reaction would have less tendency to occur in crops, and could even be a continuous feature of the work if another new tube were used before all the toxic agent had been removed from the old one.

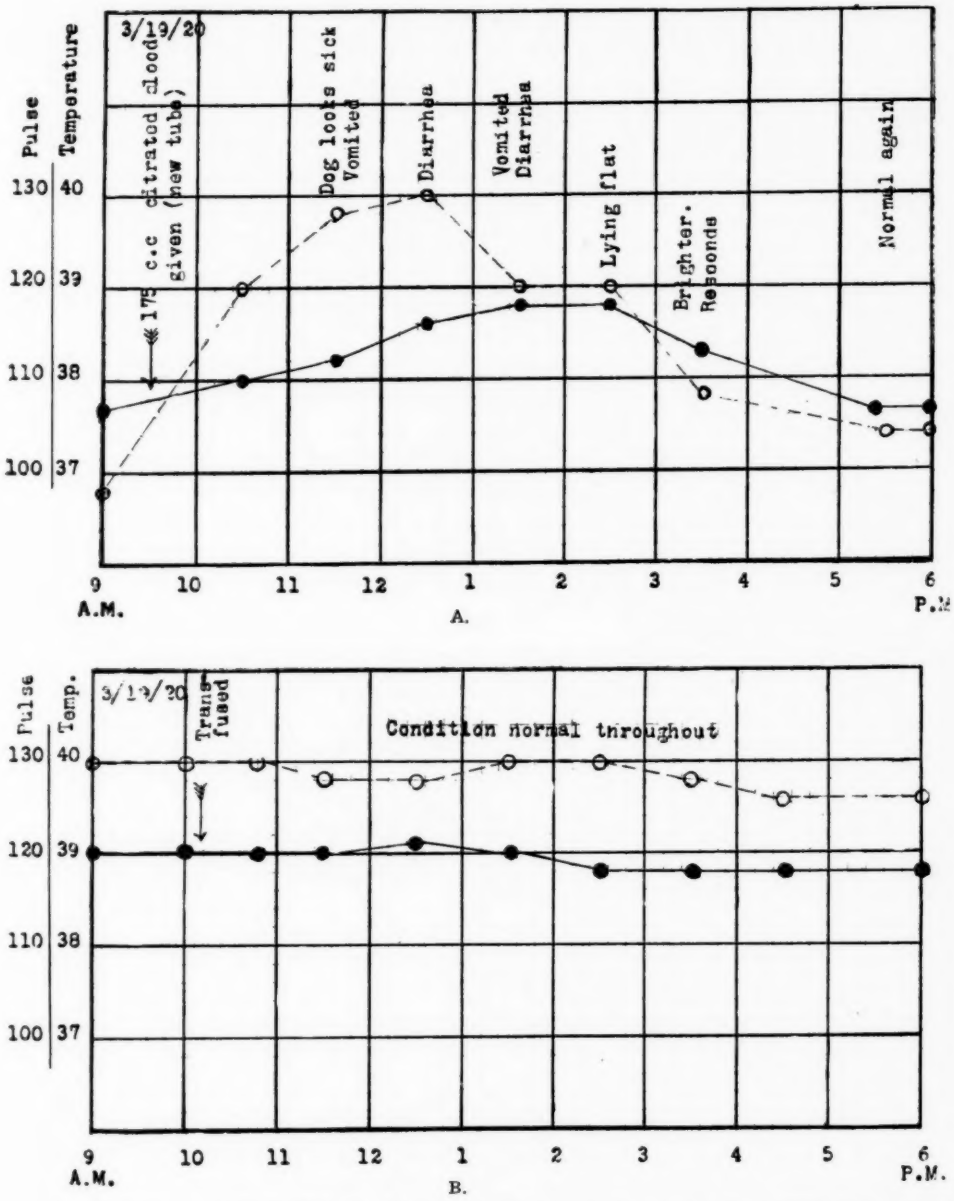

Chart 2.—*A*. Tubing reaction in a dog transfused through a sterilized new "pure gum rubber" tube with 175 c.c. of his own citrated blood. Note the fever, rise in pulse rate, vomiting and diarrhea. *B*. Control dog, which received an equal amount of his own citrated blood through "pure gum rubber" tube that had been in use for some time. Absolutely no reaction occurred. Solid line temperature; broken line pulse, in both charts.

The striking success of our efforts to duplicate in dogs the reactions following intravenous injections of arsphenamine led me to use the dog in my study of the transfusion reaction. In order to approach as nearly as possible the technic of transfusion in man, the experiments were performed with rigid asepsis. The glassware used was Pyrex or Jena. About 80 cm. of the gum rubber tubing of 4 mm. internal diameter used in routine transfusion work were employed. This tubing is identical with that employed in our arsphenamine work. It was boiled for one-half hour and rinsed before using. Old tubing was used as a control against the new in each experiment. Blood was drawn with continuous stirring

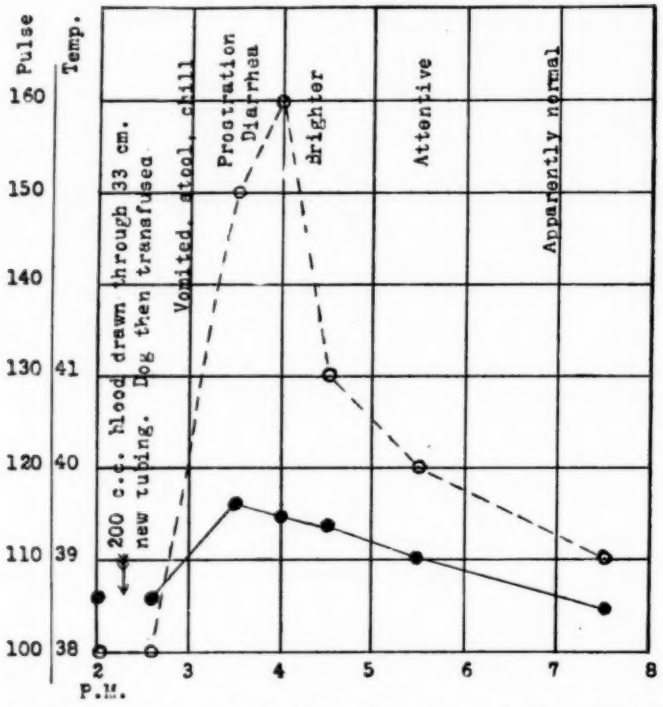

Chart. 3.—Tubing reaction in a dog transfused with 200 c.c. of his own titrated blood that had been drawn from the vein to the container of sodium citrate solution through a sterilized new "pure gum rubber" tube, 35 cm. in length. Note the chill, fever, diarrhea, vomiting, and prostration characteristic of the tubing reaction. A control dog that was transfused with 200 c.c. of his own citrated blood that had been drawn from the vein to the container of sodium citrate solution through an equal length of an old tube, showed no effect. Solid line temperature, broken line pulse.

into sterile flasks containing 2 per cent sodium citrate solution until a concentration equivalent to 30 c.c. of citrate solution to 250 c.c. of blood was reached. In every instance, each dog was transfused with his own blood. Experiments as follows were performed:

Experiment 1.—Two large healthy dogs were each transfused with 175 c.c. of their own citrated blood, one through a new piece of tubing and the other through a used piece of the same tubing. The dog that received his own blood through the new tubing developed a severe reaction. The dog that received his own blood through the used tube showed no change of pulse rate and temperature, and gave no clinical evidence of a reaction. About one hour after the injection the reacting dog showed a rise of pulse rate and temperature followed by

nausea, vomiting, diarrhea with tenesmus, prostration, rigor and tremors (Chart 2). The total rise in temperature was one degree centigrade and the increase of pulse rate, 30 per minute, the highest points being reached from three to four hours after the injection. The reaction subsided in about six hours.

Experiment 2.—The dog that had received his own blood through an old tube one week before, was given it through a new piece of tubing. A reaction occurred, although by the use of an old tube this dog had escaped reaction in the previous transfusion. In the same manner the dog that received his own blood through an old tube and showed no reaction had reacted severely the previous week to his own blood through a new tube.

Experiment 3.—A piece of the new tubing, 33 cm. long, was attached to a cannula inserted into the jugular vein of a dog and 200 c.c. of blood drawn through it from the vein to the flask containing the citrate solution. The same dog was then transfused with this blood through an old tube and a severe reaction resulted (Chart 3). This reaction began in about one-half hour with nausea, vomiting, rigor, diarrhea with cramps, sudden rise in temperature and pulse rate, followed by severe prostration. All evidence of the reaction disappeared in about six hours. The control dog whose blood was drawn through an old tube, citrated, and transfused through an old piece of tubing, showed no ill effects. It is apparent, therefore, that blood can take up the toxic agent from the tubing before citration, merely in passing from the vein to the container of citrate solution.

Experiment 4.—Two dogs each received 100 c.c. of a 0.23 per cent sodium citrate solution, one through a new tube and the other through an old one. The dog receiving the injection through the new tube developed a fatal reaction (Chart 4) characterized by vomiting, nausea, diarrhea with cramps, chills, rise in temperature and pulse rate, and prostration with death in three hours after injection.

Necropsy findings in this animal revealed only a severe, passive congestion of all organs, together with marked hemorrhages into the intestinal canal. The control dog that received the same amount of the sodium citrate solution through a used tube showed no effect.

Experiment 5.—The scrapings, dust, and debris mechanically removable from the inside of a sterilized tube, even when present in sufficient quantity to produce visible turbidity, induced no reactions in dogs when injected in suspension in distilled water, or 0.18 per cent sodium hydroxide solution, through a used tube.

Experiment 6.—Two hundred cubic centimeters of neutral redistilled water injected intravenously into dogs through new tubing induced no reaction.

Our previous observations have indicated that new tubing can be rendered harmless and incapable of producing reaction by soaking for six hours in normal sodium hydroxide solution.

SUMMARY

1. The brand of supposedly pure gum rubber tubing which in preliminary experiments by Stokes and Busman produced reaction in arsphenamine administration is apparently also able, when new, to produce reaction if used in blood transfusion work.

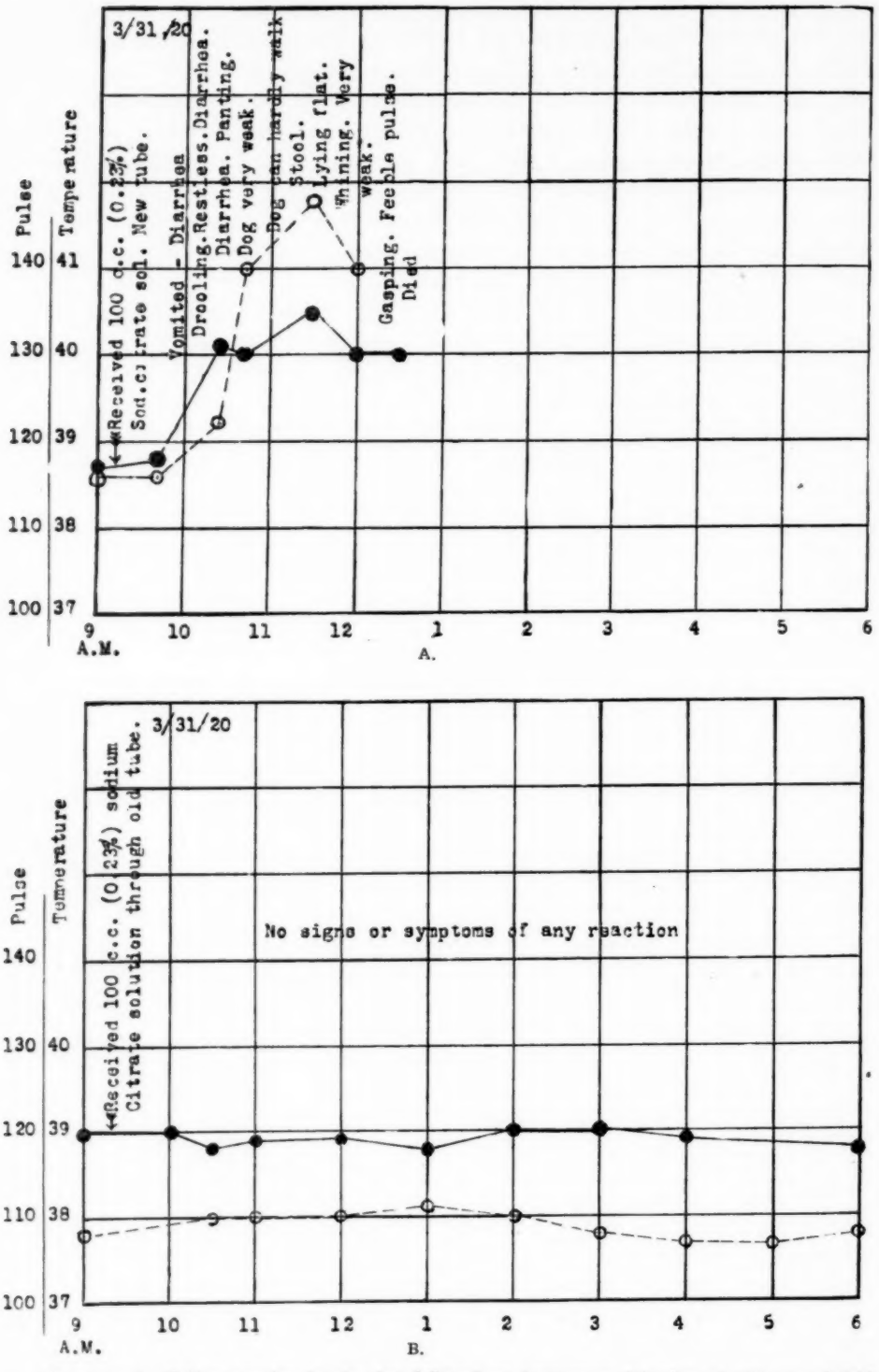

Chart 4.—*A*. Tubing reaction in the dog followed an intravenous injection of 100 c.c. of 0.23 per cent sodium citrate solution given through a new "pure gum rubber" tube. Note the vomiting, diarrhea, fever, high pulse rate, prostration and death. *B*. Control dog that received an equal dose of the same sodium citrate solution, but through a used "pure gum rubber" tube. Absolutely no reaction occurred. Solid line temperature; broken line pulse.

2. The toxic substance is taken up in sufficient amounts to produce reaction in patients receiving transfusions of citrated blood through 80 cm. of new rubber tubing of 4 mm. internal diameter.

3. Enough of the toxic agent is taken up by 250 c.c. of normal uncitrated blood drawn through as little as 35 cm. of new tubing (internal diameter 4 mm.) enroute from the vein to the container of citrate solution, to produce marked reaction when given through an old tube. It is not, therefore, necessary that whole blood be citrated to absorb the toxic principle.

4. The mechanically removable debris from the inside of new sterilized tubing does not produce reactions when given in suspension in distilled water or 0.18 per cent sodium hydroxide solution.

5. Further experiment confirms the observations previously recorded, that the toxic agent can be removed from the new tubing by soaking it in normal sodium hydroxide solution for six hours.

6. It should be specifically stated that no attempt is made to propose rubber tubing as an explanation of all transfusion reactions which present chills, fever, prostration, and so forth. Tubing is merely proposed as one factor.

7. The identity and toxicology of the poisonous principle is under investigation.

I desire to acknowledge the cooperation of my Chief, Dr. John H. Stokes, in the arrangement of this material.

CHEMICAL CHANGES IN THE BLOOD IN DISEASE*

V. Carbon Dioxide Combining Power

By Victor C. Myers, Ph.D., New York City

ALTHOUGH the phenomena of acidosis or acid intoxication would now appear to have been satisfactorily explained, it is only within the past five or six years that this has been accomplished. Progress in this subject has been particularly rapid since the advent of chemical methods of blood analysis. Of the different methods suggested to serve as an index of the degree of acidosis, the CO_2-combining power of the blood would appear to give the most reliable as well as the most useful information. The introduction by Van Slyke[1, 2] of a relatively simple method of estimating the CO_2-combining power of blood plasma has given considerable impetus to the use of this determination as a practical clinical method. It is the object of the present paper to touch upon only the salient features of acidosis with particular emphasis on this method. For a more detailed discussion, reference may be made to the paper of Van Slyke and Cullen.[3]

The term acidosis, although originally coined by Naunyn to apply to the ketosis of diabetes, has come to be used in a much broader sense with the development of our knowledge of this subject. Obviously, acidosis may result either from an abnormal formation of acid substances, such as is found in diabetes, or from a decreased elimination of normally formed substances, as in nephritis. Under conditions of health, the blood is uniformly maintained at a constant slightly alkaline reaction through the influence of the bicarbonate, phosphate and proteins of the blood.

The carbonates of the blood have been called by L. J. Henderson the first line of defense. Increased pulmonary ventilation, as occurs with dyspnea or hyperpnea, serves to increase the excretion of carbon dioxide, thus keeping the reaction of the blood within normal limits. In conditions of acidosis, other acids may combine with the bicarbonate, robbing the body of its alkali reserve. Under ordinary conditions, however, the kidneys are able to secrete an acid urine from a nearly neutral blood through the medium of acid phosphate, constituting a second means of defense. From the investigations of Marriott and Howland[4] it appears that it is just this factor which breaks down in the acidosis of nephritis. They have found the inorganic phosphates of the blood serum increased to many times the normal in nephritic acidosis, although nephritic cases without acidosis did not show this change. Other means of defense against acidosis are the blood and body proteins, which are able to take up considerable amounts of acids without marked change in reaction, and the ability to form alkali, i. e., ammonia. The latter factor is of considerable importance in the

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acidosis of such conditions as diabetes and pernicious vomiting, but apparently of little significance in nephritis.[5]

DETERMINATION OF DEGREES OF ACIDOSIS

A number of different criteria have been suggested as a measure of the degree of acidosis: (1) lowered carbon dioxide combining power of the blood; (2) lowered alveolar carbon dioxide tension; (3) decreased affinity of hemoglobin for oxygen; (4) reduced alkalinity of the blood (Sellard's test); (5) increased hydrogen-ion concentration of the blood; (6) increased intensity of urinary acidity (hydrogen-ion concentration), and (7) the retention of alkali by the body in cases in which the kidney is capable of rapidly excreting an excess of alkali. Yandell Henderson[6] has also suggested the very simple test of holding the breath. A normal person can hold the breath 30 to 40 seconds without an especially deep inspiration, but the period diminishes in proportion to the reduction in the blood alkali.

All of these methods have furnished valuable information in the development of our knowledge of this subject, but the first, second and seventh have yielded information of special clinical value. Although the carbon-dioxide tension of the alveolar air may readily be ascertained with the Friderica[7] or the Marriott apparatus,[8] the information is not as reliable as the carbon dioxide combining power of the blood determined by the Van Slyke method. That the bicarbonate depletion may roughly be determined by administration of sodium bicarbonate has been pointed out by Sellards,[9] and by Palmer and Henderson,[10] and this method has been in practical use for several years. Normally from 5 to 10 gm. of sodium bicarbonate are sufficient to change the reaction of the urine, but in acidosis of advanced nephritis the deficiency may amount in exceptional instances to as much as 100 gm. of bicarbonate or more.

Palmer and Van Slyke[11] have recently studied this question in connection with the carbon dioxide combining power of the blood. They found that in most pathologic cases the urine did not become more alkaline than blood until a higher plasma bicarbonate had been reached than in normal individuals. This would result in the giving of unnecessary and possibly injurious amounts of bicarbonate, if the administration was continued until the urine turned alkaline, as has

TABLE I

THE CO_2-COMBINING POWER OF BLOOD PLASMA IN NORMAL SUBJECTS AND IN ACIDOSIS*

CONDITION OF SUBJECT	CO_2 CAPACITY OF PLASMA	FURTHER DROP OF CO_2 PERMITTED BEFORE INTERRUPTING FAST IN ALLEN TREATMENT OF DIABETES
	c.c. to 100	
Normal resting adult,** extreme limits	77-53	To 45 volume per cent
Mild acidosis, no visible symptoms	53-40	Drop of 10 to 5 volume per cent
Moderate acidosis, symptoms may be apparent	40-31	Drop of 3 to 2 volume per cent
Severe acidosis, symptoms of acid intoxication	Below 31	Fast interrupted in 6 to 12 hours unless CO_2 rises with fasting and alkali
Lowest CO_2 observed with recovery	16	

*Compiled from Stillman, Van Slyke, Cullen and Fitz,[13] and Allen, Stillman and Fitz.[14]
**The figures for normal infants are about 10 volume per cent lower.

been the usual clinical procedure. The bicarbonate retention may therefore indicate a much more severe acidosis than actually exists. Palmer and Van Slyke advise carefully controlling the therapeutic use of sodium bicarbonate. They have calculated that taking 42 pounds as the unit of weight, 0.5 gm. of sodium bicarbonate will raise the plasma carbon dioxide 1 per cent by volume. In view of this, it is possible to calculate the amount of alkali required to restore the plasma bicarbonate to normal.

The normal range for the carbon dioxide combining power of the blood in the adult, as shown by Van Slyke, Stillman, and Cullen,[12] is from 53 to 77 c.c. of carbon dioxide per hundred c.c. of plasma. For normal infants the figures are about 10 c.c. lower than in adults. An idea of the findings for the CO_2 in acidosis of varying degrees of severity may be obtained from Table I.

ACIDOSIS IN DIABETES

That acetone bodies appear in the urine in large amounts in cases of diabetes with acidosis has long been recognized and their amount taken as an index of the acidosis. Later it was noted that these cases showed a high output of ammonia and this was likewise employed to determine the severity of the acidosis. As indicated above, these findings led to some confusion because they could not be applied to the acidosis of nephritis. The defective oxidation of the fats in diabetes results in the formation of the acetone bodies, acetone, diacetic acid and β-hydroxybutyric acid. The reaction of these organic acids with the sodium bicarbonate of the blood, results in the taking up of sodium by the acids and the setting free of the CO_2, thus robbing the body of its alkaline reserve. What may happen in this respect in diabetes is shown in Table II.

TABLE II

ILLUSTRATIVE FINDINGS FOR THE CO_2-COMBINING POWER OF BLOOD PLASMA IN DIABETES

CASE	AGE	SEX	DATE	CO_2 COMBINING POWER	BLOOD SUGAR	REMARKS
				c.c. to 100	per cent	
1. B. S.	46	♀	8/25/15	12	0.42	Death in coma
2. U. W.	49	♂	2/27/19	25	0.79	Death in coma
			3/ 1/19	12	1.33	
3. A. F.	20	♂	11/12/18	32	0.86	Marked lipemia, Cholesterol 0.64 per cent, left hospital improved
			11/19/18	39	0.41	
4. J. G.	51	♀	6/20/19	59	0.24	Improved
			6/28/19	46	0.24	
			7/ 7/19	55	0.25	
5. R. G.	45	♀	9/11/17	36	0.22	Improved
			9/18/17	52	0.20	
			10/ 9/17	53	0.19	
6. M. B.	27	♀	2/ 9/17	33	0.22	Marked improvement
			2/16/17	45	0.23	
			2/20/17	55	0.19	
			2/27/17	54	0.16	
			3/ 9/17	50	0.18	
			3/27/17	60	0.14	

The first two cases died in diabetic coma with CO_2-combining power figures of 12. Case 3 illustrates the findings in a case of severe diabetes, who was still up and about. This patient was referred to the writer (as a member of the Medical

Advisory Board) as to his availability for the Army, although the fact that he had diabetes was known. Except for shortness of breath and slightly impaired vision, this patient appeared to feel very well. At his own request he was admitted for a short stay in the hospital. The data on Case 4 and 5 illustrate the findings in the average case of diabetes, the latter showing a moderate acidosis. In Case 6 there was a gradual restoration of both the CO_2 and sugar to practically normal.

The body is ordinarily able to handle quite large amounts of acids without a marked drop in the alkaline reserve. The tests for acetone and diacetic acid in the urine in diabetes and other conditions are valuable diagnostically, but they tell little concerning the severity of the acidosis. To secure this information it is necessary to resort to such tests as the carbon dioxide combining power of the blood.

In the treatment of diabetes, in particular by the Allen method so commonly employed, acidosis is more to be feared than hyperglycemia, and should be more carefully followed. With the fasting treatment the hyperglycemia is obviously effectively combated, but sometimes, as pointed out by Allen, Stillman and Fitz,[14] patients react to fasting with an increase of acidosis, occasionally to a dangerous degree. Rules which they have laid down to follow as to the drop in CO_2 permissible in this connection are given in Table I.

Both Allen and Joslin are opposed to the extensive use of sodium bicarbonate in the treatment of diabetic acidosis, believing that when not severe the condition may be more satisfactorily treated in other ways. Allen states[14] that fasting checks the acetone body formation and that accordingly the great majority of cases of acidosis can be treated by this means alone, and alkali holds no more than a minor adjuvant position. He has shown, however, that occasionally its use is of definite value either in combating a long and stubborn acidosis, or in combating coma in certain severe cases. Here it may save life.

ACIDOSIS IN NEPHRITIS

Many cases of renal disease show a more or less pronounced acidosis. In a recent report Chace and Myers[15] have concluded that all fatal cases of chronic nephritis with marked nitrogen retention show a severe acidosis, sufficient in many instances to be the actual cause of death. Their experience would lead them to believe that not even moderately severe acidosis was encountered in cases of nephritis without considerable nitrogen retention. Cases of acute nephritis may occasionally show a severe acidosis. To illustrate the importance of acidosis in nephritis, three groups of two cases each are tabulated in Table III. The first two patients suffered from severe chronic nephritis, showing marked nitrogen retention and acidosis. It is worthy of note that Case I was up and about at the time of the first analyses, while Case 2 after a short stay in the hospital, was at home for a period of seven weeks feeling improved. In both of these cases there was a very severe acidosis, and at the end the CO_2 dropped to such a low level as to be incompatible with life. The observations of Whitney[16] make it evident that such low figures may be the direct cause of death. As these patients did not receive alkali (until after the last recorded test), the CO_2 obviously fell to a

TABLE III

ACIDOSIS IN CHRONIC AND ACUTE NEPHRITIS*

CASE	AGE	SEX	DATE	CO_2 COMBINING POWER C.C. PER 100	CREATININE, MG. PER 100 C.C. BLOOD	UREA NITROGEN, MG. PER 100 C.C. BLOOD	REMARKS
1. E. M.	39	♂	11/30/15	24	17.5	97	
			12/ 4/15	21	21.5	129	
			12/10/15	26	22.3	132	
			12/17/15	15	24.2	150	
			12/24/15	12	26.7	200	Death in chronic nephritis apparently due to acidosis; no alkali given
2. A. N.	27	♀	3/12/18	31	8.6	97	
			3/26/18	28	12.1	110	
			4/16/18	23	11.2	78	
			5/ 7/18	25	15.2	76	
			5/24/18	12	17.0	148	
3. W. W.	30	♂	2/11/16	23	8.5	55	
			2/23/16	21	12.5	76	
			3/ 7/16	52	10.4	60	Acute exacerbation of chronic nephritis; clinical improvement coincident with rise in alkali reserve; alkali given for a time
			4/ 7/16	54	9.5	39	
			5/10/16	22	9.6	56	
4. J. McC.	56	♂	12/28/15	20	5.1	64	
			1/ 8/16	56	4.5	39	
			1/11/16	58	5.4	39	
			2/ 4/16	40	4.8	36	
5. M. McA.	44	♂	1/25/16	22	4.6	71	
			4/11/16	45	2.7	17	
			5/ 8/17	..	2.4	17	
6. W. C.	49	♂	1/15/16	22	3.5	44	Severe acidosis in acute nephritis with complete recovery
			1/17/16	58	4.1	62	
			1/19/16	56	3.2	53	
			1/28/16	..	1.9	19	
			6/11/18	..	1.8	16	

*Taken from Chace and Myers.[15]

lower level than would otherwise have been the case. The findings in these two cases are the lowest we have encountered, the figures more often falling between 20 and 30 during the last days of life.

Cases 3 and 4 on admission to the hospital showed pronounced symptoms of acidosis. Although both patients died about one month after leaving the hospital, they showed considerable clinical improvement, this being coincident with the rise in the CO_2-combining power of the blood plasma.

The last two patients were cases of acute nephritis, showing severe acidosis (very marked dyspnea), but ending in complete recovery. Although this type of case is apparently not frequently encountered, it furnishes an interesting contrast to the preceding two groups. Case 6 was admitted supposedly in "uremic" coma. On estimating the blood creatinine and urea, however, we were surprised at the comparatively slight nitrogen retention, but an estimation of the CO_2 of the blood plasma disclosed the apparent difficulty. Two infusions of sodium bicarbonate, 12 grams each, on the fifteenth and sixteenth produced quite remarkable clinical results, and in less than two weeks the blood findings were normal.

That cases of Asiatic cholera develop a severe acute nephritis and a fairly large percentage, uremia is well known. Sellards[17] has obtained most favorable results by the administration of alkali to these cases, markedly lowering the mortality rate.

It may also be noted here that cases of severe pneumonia frequently show considerable nitrogen retention, and often severe acidosis, as shown by the CO_2-combining power of the blood. We have many observations in substantiation of this.

ACIDOSIS FINDINGS IN CHILDREN

The subject of acidosis occurring with infantile diarrhea is one that has recently received considerable attention, especially at the hands of Howland and Marriott,[18] Chapin and Pease,[19] and Schloss and Stetson.[20] Howland and Marriott have shown that the acidosis found in many cases of severe diarrhea not of the ileocolitis type is not due to the presence of acetone bodies, but apparently is due to deficient excretion of acid phosphate by the kidneys, as is the case in nephritis. The administration of sodium bicarbonate will often bring about a cessation of the almost characteristic hyperpnea and cause the laboratory tests to give results that are found with normal infants. Nevertheless, the child may die. Schloss and Stetson have applied the Van Slyke method to a quite extensive series of cases. In 27 normal cases the figures ranged from 46 to 63 c.c. CO_2 per 100 c.c. of plasma, while in 17 out of 19 cases of diarrhea with toxic symptoms his figures ranged from 13 to 38. The acetone bodies of the blood have been studied by Moore.[21] In cases of diarrhea without ileocolitis there is only a moderate increase in acetone bodies, while with ileocolitis the amount of acetone bodies is very large.

TABLE IV

CASES ILLUSTRATING ACIDOSIS IN CHILDREN*

CASE	AGE	SEX	DATE	CO_2 COMBINING POWER	BLOOD SUGAR per cent	DIAGNOSIS, REMARKS
	mo.			c.c. to 100		
1. A. N.	2	♀	9/26/15	22	0.09	Gastroenteritis; acidosis; death
2. W. R.	3 1/2	♂	1/20/15	24	0.10	Gastroenteritis; acidosis; death
3. Y. W.	1 1/2	♀	11/ 9/17	24	....	Gastroenteritis; acidosis; death
4. M. K.	10	♂	10/19/17	25	....	Gastroenteritis; acidosis; death
5. J. T.	4	♂	10/13/15	26	0.10	Malnutrition; recovery
6. H. C.	8 1/2	♂	11/15/15	28	0.09	Malnutrition; acidosis; recovery
7. J. M.	12	♀	11/ 3/17	28	....	Gastroenteritis and rickets; vomiting; improvement
8. P. K.	10	♀	11/24/15	33	0.11	Lobar pneumonia; acidosis; death

*Taken from Chapin and Myers.[22]

Table IV presents observations on a few of our cases. It will be noted that the plasma CO_2 ranged from 22 to 25 in the first four cases and that these cases all proved fatal.

ACIDOSIS AS THE RESULT OF ANESTHESIA

It is a matter of common observation that urine voided following ether anesthesia gives positive tests for acetone bodies in the urine. More recently it has been shown by Morriss,[23] and others that the anesthesia results in a lowering of the CO_2-combining power of the blood. From this coincidence it was natural to attribute the decreased alkaline reserve to the acetone body formation. Experiments carried out by Short[24] in this laboratory indicate, however, that acetone bodies are not formed promptly enough during the anesthesia to account for the decreased plasma bicarbonate. Data are given in Table V on illustrative cases showing the CO_2-combining power of blood plasma before and after ether anesthesia. As will be noted the drop in CO_2 ranged from 4 to 17 volume per cent. From these observations it is apparent what would happen if cases

TABLE V

INFLUENCE OF ETHER ANESTHESIA ON THE CO_2-COMBINING POWER OF BLOOD PLASMA*

CASE	AGE	SEX	CO_2 COMBINING POWER c.c. to 100 c.c.		TIME OF ANESTHETIC	OPERATION
			PREOPERATIVE	POSTOPERATIVE		
					min.	
1. E. C.	36	♂	53	49	26	Hemorrhoidectomy
2. W. D.	37	♂	69	60	40	Inoperable carcinoma of stomach
3. E. C.	51	♀	51	45	45	Femoral hernia
4. M. B.	36	♀	54	40	70	Carcinoma of the breast
5. W. C.	50	♂	62	52	43	Inoperable carcinoma of bladder
6. S. A.	40	♀	58	41	43	Right nephrectomy

*Taken largely from Short.[24]

of severe diabetes or nephritis with low figures for the CO_2 were operated on under general anesthesia. According to Morriss the drop in the CO_2 is more pronounced after chloroform than ether. A few unpublished observations which have been collected by Killian in this laboratory indicate that the drop in CO_2 is much less after spinal or gas-oxygen anesthesia. Morriss has pointed out that the preliminary administration of sodium bicarbonate increases the alkali reserve, although the most noteworthy effect of this treatment is to lead to higher values for this factor of safety at the conclusion of the anesthetic. Another method of combating the postoperative acidosis has been suggested by Henderson, Haggard and Coburn,[25] viz., the administration by inhalation of carbon dioxide properly diluted with air. This serves for one thing to increase the breathing and more rapidly remove the anesthetic from the blood, also to restore the preoperative CO_2-combining power.

ESTIMATION OF THE CO_2-COMBINING POWER OF THE BLOOD

As already pointed out, the estimation of the carbon dioxide combining power of the blood is probably the most reliable means of ascertaining the severity of acidosis. We have long had methods of estimating the CO_2 of the blood, although the subject did not receive much attention previous to the work of Barcroft and Haldane.[26] Many important contributions have emanated from

Haldane's laboratory, but it remained for Van Slyke[2] to develop a method so simple that it could readily be employed for clinical purposes. For the extraction of the gas, Van Slyke has made use of a Torricellian vacuum, with which the gas is easily and completely extracted in a closed chamber without any loss. The objection has been raised to the Van Slyke method that determinations made on plasma are not as reliable an index of acidosis[27] as those obtained with whole blood. (The Van Slyke method may be employed for whole blood, but the apparatus is easily gummed up and not readily cleaned.) Henderson and Morriss[27] have described a method of gas analysis, which may be applied to whole blood as well as plasma. Their method is, however, theoretically less exact than that of Van Slyke. That the CO_2 tension of the alveolar air yields results that are evidently less reliable than the CO_2-combining power of blood plasma is brought out in data presented by Peters.[28]

In the Van Slyke method the plasma from oxalated blood is shaken in a separatory funnel filled with an air mixture, the CO_2 tension of which approximates that of normal arterial blood. In this way it is combined with as much CO_2 as it is able to hold under normal tension. A known quantity of the saturated plasma is then acidified within the gas pipette, and its CO_2 liberated by the production of a partial vacuum. The liberated CO_2 is then placed under atmospheric pressure, its volume carefully measured and the volume corresponding to 100 c.c. of plasma calculated.

Method[2, 3]—The blood plasma may be obtained from the blood specimen collected for routine blood analysis as already described* provided a portion of this specimen is centrifuged as soon as secured.** The plasma is then pipetted off. Better, the blood may be drawn into a special centrifuge tube containing a little powdered potassium oxalate under some paraffin oil (see Fig. 1). By a gentle rotating motion the blood is mixed with the oxalate and then centrifuged as soon as possible, and the plasma pipetted off. In case the CO_2 capacity cannot be determined at once, the plasma is transferred to a paraffin lined tube, covered with oil, stoppered and placed on ice where it will keep unchanged for a week.

To determine the CO_2-combining power, the plasma is saturated with carbon dioxide at alveolar tension. This can conveniently be done by placing about 3 c.c. of plasma (at room temperature) in a separatory funnel of about 300 c.c. capacity, and the funnel filled with alveolar air from the lungs of the operator. In order to bring the moisture content down to saturation at room temperature, the air is passed through a bottle full of glass beads before it enters the funnel (see Fig. 1). The operator, without inspiring more deeply than normal, expires as quickly and as completely as possible through the glass beads and separatory funnel. The funnel is closed just before the expiration is finished, and is shaken for one minute in such a way that the plasma is evenly distributed about the walls, forming a thin layer which quickly approaches equilibrium with the CO_2 in the air. After the shaking has lasted a minute, a fresh portion of alveolar air is run into the funnel and the shaking completed. The funnel is now placed in an upright position so that the plasma may drain into the narrow space at the bottom of the funnel and from which it may be readily pipetted.

The Van Slyke apparatus is illustrated at the left in Fig. 1. It consists essentially of a 50 c.c. pipette with three-way stopcocks at top and bottom, and a 1 c.c. scale on the upper stem, divided into 0.02 c.c. divisions. The bottom of the apparatus is connected with a leveling bulb filled with mercury by means of a heavy walled rubber tube. The

*See page 423, Jour. Lab. and Clin. Med., on Nonprotein and Urea Nitrogen.

**Van Slyke and Cullen point out that it is desirable that the subject should avoid vigorous muscular exertion for at least an hour before the blood is drawn, and also best to avoid stasis, or when stasis is necessary to release the ligature as soon as the vein is entered and allow a few seconds for the stagnant blood to pass.

chamber, *d*, serves to draw off the solutions after the CO_2 has been extracted from them, while *c* serves for the subsequent release of the vacuum by the entrance of mercury. The apparatus is made of strong glass, in order to stand the weight of mercury without danger of breaking, and is held in a strong screw clamp, the jaws of which are lined with thick pads of rubber. To prevent accidental slipping of the apparatus from the clamp, an iron rod covered with a piece of rubber tubing should be so arranged as to project under cock *f* and between *c* and *d*. Capillary *a* is used for convenient removal of solutions from the apparatus. It is of advantage to have a small large-necked bottle clamped to the stand in such a position as to be under the mouth of this tube. Three hooks or rings at the level 1, 2, and 3 serve to hold the leveling bulb at different stages of the analysis. Practically the only source of difficulty with the apparatus is in the entrance of air through the stopcocks. It is essential, therefore that both cocks should be properly greased (a mixture of paraffin and vaseline works very well) and air tight. It is also necessary that the cocks (especially *f*) should be held in place so that they cannot be forced out by pressure of the mercury. For this purpose strong rubber bands work very well.

Before beginning a determination it is necessary to test the apparatus for tightness and freedom from gases. The entire apparatus (Fig. 1), including the capillaries above the upper stopcock, is filled with mercury, and the mercury bulb then lowered to position 3, so that a Torricellian vacuum is obtained, the mercury falling to about the middle of *d*. The leveling bulb is then raised again. If the apparatus is tight and gas-free the mercury will refill it completely and strike the upper stopcock with a sharp click, but in case there is any gas in the apparatus this will serve as a cushion. Should this be the case, the apparatus must be repeatedly evacuated until the gas has all been removed.

For the determination, the apparatus, including both capillaries above the upper stopcock, is entirely filled with mercury by placing the leveling bulb of mercury in position 1, and turning stopcock *c*. The cup at the top is next washed free of acid with carbonate-free ammonia water,* by employing a few drops of the ammonia water, a drop of phenolphthalein and about 1 c.c. of distilled water. This is then all removed but a drop or two, with the aid of a pipette. With an Ostwald-Folin pipette 1 c.c. of the plasma from the separatory funnel is allowed to run into the cup *b* of the apparatus, the tip of the pipette remaining below the surface of the solution in the cup during the transfer, and under the thin film of slightly pink solution. The final drop of plasma is expressed by closing the top of the pipette with the forefinger of one hand, and warming the bulb with the palm of the other.

With the mercury bulb at position 2 and the stopcok *f* in the position shown in the figure, the plasma is admitted from the cup into the 50 c.c. chamber, leaving just enough above the stopcock *e* to fill the capillary so that no air is introduced when the next solution is added. The cup is now washed with two portions of about 0.5 c.c. each of water, care being taken that no air enters the apparatus. A small drop (about 0.02 c.c.) of caprylic alcohol is next added to the cup and permitted to flow entirely into the capillary above *e*, and finally 0.5 c.c. of 5 per cent sulphuric acid is run in. It is not necessary that exactly 1 c.c. of wash water and 0.5 c.c. of acid shall be used, but the total volume of the water solution introduced must extend exactly to the 2.5 c.c. mark on the apparatus if the special formulas of Van Slyke and Cullen in Table VI are to be used. After the acid has been admitted a drop of mercury is placed in *b* and allowed to run down the capillary as far as the stopcock in order to seal the latter. Whatever excess of the sulphuric acid remains in the cup is washed out with a little water.

The mercury bulb is now lowered and hung at position 3, and the mercury in the pipette is allowed to run down to the 50 c.c. mark, producing a Torricellian vacuum in the apparatus. When the mercury (not the water) meniscus has fallen to the 50 c.c. mark, the lower cock is closed, and the pipette is removed from the clamp. Equilibrium of the CO_2 between the 2.5 c.c. of water solution and the 47.5 c.c. of free space in the apparatus is obtained by turning the pipette upside down fifteen or more times, thus thoroughly agitating its contents. The pipette is then replaced in the clamp. By turning the lower

*It is convenient to have a set of five dropping bottles with ground in pipettes and rubber bulbs. The set consists of 1 per cent carbonate-free ammonia water, 1 per cent alcoholic phenolphthalein, *distilled* water, caprylic alcohol and 5 per cent sulphuric acid.

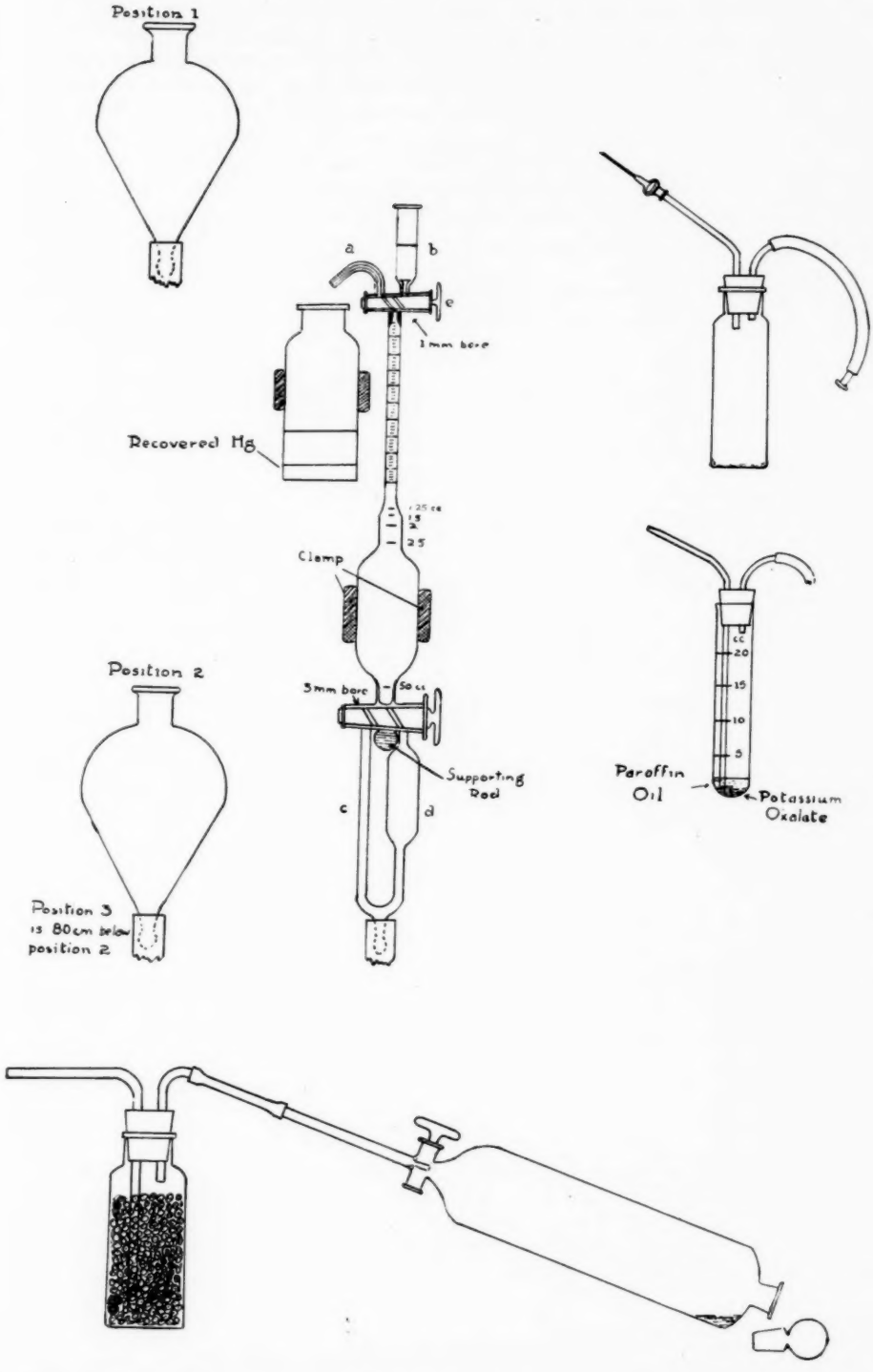

Fig. 1.—Showing Van Slyke apparatus at left, blood bottle and centrifuge tube employed in collecting blood at right, and apparatus used in saturating blood plasma with carbon dioxide.

stopcock, *f*, the water solution is now allowed to flow from the pipette completely into *d* without, however, allowing any gas to follow it. The leveling bulb is then raised in the left hand, while with the right the stopcock is turned so as to connect the pipette with *c*. The mercury flowing in from *c* fills the body of the pipette, and as much of the calibrated stem at the top as is not occupied by the gas extracted from the solution. A few hundredths of a c.c. of water which could not be completely drained into *d* float on top of the mercury in the pipette, but the error caused by reabsorption of carbon dioxide into the small volume of water is negligible if the reading is made at once. The mercury bulb is placed at such a level that the gas in the pipette is under atmospheric pressure, and the volume of the gas is read off on the scale. In order to have the column in the pipette exactly balanced by that outside, the surface of the mercury in the leveling bulb should be raised until it is level with the mercury meniscus in the pipette, and then, for entire accuracy, raised above the latter meniscus by a distance equal to 1/14 the height of the column of water above the mercury in the pipette.

TABLE VI

TABLE FOR CALCULATION OF CO_2-COMBINING POWER OF PLASMA*

OBSERVED VOL. GAS $\times \frac{B}{760}$	C.C. OF CO_2, REDUCED TO 0°, 760 mm., BOUND AS BICARBONATE BY 100 C.C. OF PLASMA.				OBSERVED VOL. GAS $\times \frac{B}{760}$	C.C. OF CO_2, REDUCED TO 0°, 760 mm., BOUND AS BICARBONATE BY 100 C.C. OF PLASMA.			
	15°	20°	25°	30°		15°	20°	25°	30°
0.20	9.1	9.9	10.7	11.8	0.60	47.7	48.1	48.5	48.6
1	10.1	10.9	11.7	12.6	1	48.7	49.0	49.4	49.5
2	11.0	11.8	12.6	13.5	2	49.7	50.0	50.4	50.4
3	12.0	12.8	13.6	14.3	3	50.7	51.0	51.3	51.4
4	13.0	13.7	14.5	15.2	4	51.6	51.9	52.2	52.3
5	13.9	14.7	15.5	16.1	5	52.6	52.8	53.2	53.2
6	14.9	15.7	16.4	17.0	6	53.6	53.8	54.1	54.1
7	15.9	16.6	17.4	18.0	7	54.5	54.8	55.1	55.1
8	16.8	17.6	18.3	18.9	8	55.5	55.7	56.0	56.0
9	17.8	18.5	19.2	19.8	9	56.5	56.7	57.0	56.9
0.30	18.8	19.5	20.2	20.8	0.70	57.4	57.6	57.9	57.9
1	19.7	20.4	21.1	21.7	1	58.4	58.6	58.9	58.8
2	20.7	21.4	22.1	22.6	2	59.4	59.5	59.8	59.7
3	21.7	22.3	23.0	23.5	3	60.3	60.5	60.7	60.6
4	22.6	23.3	24.0	24.5	4	61.3	61.4	61.7	61.6
5	23.6	24.2	24.9	25.4	5	62.3	62.4	62.6	62.5
6	24.6	25.2	25.8	26.3	6	63.2	63.3	63.6	63.4
7	25.5	26.2	26.8	27.3	7	64.2	64.3	64.5	64.3
8	26.5	27.1	27.7	28.2	8	65.2	65.3	65.5	65.3
9	27.5	28.1	28.7	29.1	9	66.1	66.2	66.4	66.2
0.40	28.4	29.0	29.6	30.0	0.80	67.1	67.2	67.3	67.1
1	29.4	30.0	30.5	31.0	1	68.1	68.1	68.3	68.0
2	30.3	30.9	31.5	31.9	2	69.0	69.1	69.2	69.0
3	31.3	31.9	32.4	32.8	3	70.0	70.0	70.2	69.9
4	32.3	32.8	33.4	33.8	4	71.0	71.0	71.1	70.8
5	33.2	33.8	34.3	34.7	5	71.9	72.0	72.1	71.8
6	34.2	34.7	35.3	35.6	6	72.9	72.9	73.0	72.7
7	35.2	35.7	36.2	36.5	7	73.9	73.9	74.0	73.6
8	36.1	36.6	37.2	37.4	8	74.8	74.8	74.9	74.5
9	37.1	37.6	38.1	38.4	9	75.8	75.8	75.8	75.4
0.50	38.1	38.5	39.0	39.3	0.90	76.8	76.7	76.8	76.4
1	39.1	39.5	40.0	40.3	1	77.8	77.7	77.7	77.3
2	40.0	40.4	40.9	41.2	2	78.7	78.6	78.7	78.2
3	41.0	41.4	41.9	42.1	3	79.7	79.6	79.6	79.2
4	42.0	42.4	42.8	43.0	4	80.7	80.5	80.6	80.1
5	42.9	43.3	43.8	43.9	5	81.6	81.5	81.5	81.0
6	43.9	44.3	44.7	44.9	6	82.6	82.5	82.4	82.0
7	44.9	45.3	45.7	45.8	7	83.6	83.4	83.4	82.9
8	45.8	46.2	46.6	46.7	8	84.5	84.4	84.3	83.8
9	46.8	47.1	47.5	47.6	9	85.5	85.3	85.2	84.8
0.60	47.7	48.1	48.5	48.6	1.00	86.5	86.2	86.2	85.7

*Taken from Van Slyke and Cullen.[3]

By means of Table VI the readings on the apparatus can be directly transposed into c.c. of CO_2 chemically bound by 100 c.c. of blood plasma. This table takes into account the air which enters the apparatus dissolved in the water, etc. The barometer reading and room temperature are taken at the time of the determination. For convenience in the calculation, values are given in Table VII for the ratio $\frac{\text{barometer}}{760}$ over the range usually encountered.

TABLE VII

BAROMETER	BAROMETER / 760	BAROMETER	BAROMETER / 760
732	0.961	756	0.995
734	0.966	758	0.997
736	0.968	760	1.000
738	0.971	762	1.003
740	0.974	764	1.006
742	0.976	766	1.008
744	0.979	768	1.011
746	0.981	770	1.013
748	0.984	772	1.016
750	0.987	774	1.018
752	0.989	776	1.021
754	0.992	778	1.024

From an inspection of Table VI it will be observed that the difference between the readings and actual values of CO_2 gas bound is roughly 12. When we first began the use of their apparatus, Drs. Van Slyke and Cullen suggested to us that a correction of 12 would give sufficiently accurate results for clinical purposes, thus eliminating the use of the table or a calculation. We have frequently done this. Somewhat greater accuracy might be obtained by deducting 10 from readings 20-35, 11 from readings 36-40, 12 for readings 51-70 and 13 for readings 71-85.

After the determination has been finished, the leveling bulb is again lowered without opening the upper stopcock, and most of the mercury is withdrawn through *c*. The water solution from *d* is readmitted and, the leveling bulb being raised to position 1, the water solution, with a little mercury, is forced out of the apparatus through *a*. The apparatus is now ready for another determination. It is not necessary to wash it out, since the few drops which remain in it attached to walls hold no measurable amount of carbon dioxide. When not in use the entire apparatus should be filled with water.

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ON CHLORIDE METABOLISM*

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ALTHOUGH Justus von Liebig, the founder of the modern system of nutrition, pointed out in the middle of the last century the value of salts in the diet, and later on Voit and Forster in the "seventies" on the basis of experiments carried out by Forster, emphasized the importance of the mineral salts in the organism, the chemical investigations of metabolism have for a long time dealt chiefly with the organic food stuffs, while little interest has been evinced for the inorganic substances in the diet until the last few decades.

Among the soluble substances the chlorides are in majority in nature, and are also the most predominant in the fluids of the human organism. According to the investigations of Stuber the chlorides constitute about three-fourths of all the electrolytes in the human body.

Chlorine exists in the body chiefly combined with Na and K, partly also with Ca, Mg, and ammonium. The K salt is chiefly found in the cells, while the Na salt is for the most part in the fluids.

The importance of the chlorides is partly due to their general physicochemical influence, partly to some special qualities.

The life and activity of the protoplasm depend upon certain physicochemical qualities of the fluids in the body: fixed osmotic pressure and fixed hydrogen-ion concentration. Minimal changes in the pressure and in the hydrogen-ion concentration exist, but the changes need not be great to destroy life. Both the absorbed foodstuffs and the intermediate metabolism tend to change the pressure and the reaction of the blood and the tissue fluid, but in consequence of the rapid diffusion and the great dissociation of the salts, especially the chlorides, the osmotic pressure and the hydrogen-ion concentration are very stable.

Together with many other salts the chlorides are always to be found in the living cells, and the investigations of Loeb suggest that the chlorides are necessary for the development of the animal cell.

Like many other salts the chlorides act as catalysts, but the opinion of Voit that the chlorides influence the general metabolism has not been confirmed.

The chlorides are of special importance for the production of the hydrochloric acid of the stomach. Opinions still differ as to how this acid is produced, but its origin from the chlorides of the diet, with the chlorides of the blood serving as an intermediate link, cannot be disputed. This is proved by the fact that the production of hydrochloric acid ceases in animals on salt-free diet.

Owing to the ability of the organism to keep the osmotic pressure constant, there is an intimate correlation between chloride and water metabolism. Widal and Javal have pointed out that by great changes in the chlorides of the diet, the amount of the chlorides in the body may vary about 12 gm., while at the

*Lecture given at the University of Christiania, Christiania, Norway.

same time the water content varies 1½-2 liters. But on ordinary diet and under physiologic conditions the chloride and water content of the body are fairly constant.

Determination of the total amount of the chlorides in an adult person is not yet made. But we have several analyses of newborn children, in whom has been found an average of 0.30 per cent. If from this we calculate the amount in adults and remember that adults have a little less water and therefore also less chlorides than newborn children, we shall find that the amount of chlorides in a person weighing 70 kilos is between 100 and 200 gms.

The chlorides are found chiefly, but not exclusively, in the fluids of the body. Uncertainty still exists as to whether the chlorides exist as adsorbed to the protoplasm of the cells. Some authors are of the opinion that at least in pathologic conditions the chlorides are partly adsorbed to the cells. But all agree that the chlorides mainly circulate in dissociated compounds in the organism.

The concentration of the chlorides in the blood has been the subject of considerable research:

Blood, per cent:	0.44 Rumpf.
	0.6-0.7 Georgpulos.
	0.45-0.47 Schmidt, Wanach.
	0.49 McLean, Van Slyke.
	0.45-0.50 Gettler, Baker.
Serum, per cent:	0.46-0.58 Hefter, Siebeck.
	0.597-0.614 McLean, Van Slyke.
	0.56-0.64 Gettler, Baker.
	0.46-0.65 Myers, Fine.

By means of Bang's micro method I have examined the conceneration of the blood chlorides in several healthy men and women, as a result of which I have found the concentration to vary between 0.44 and 0.48 per cent. Bang's method is correct within 5 per cent.

The concentration of the chlorides in the serum I have found to vary between 0.55 and 0.60 per cent. This great difference between the concentration in blood and serum shows that the chlorides exist chiefly in serum, to a much less degree in the corpuscles.

It has been impossible to determine the chloride concentration of the tissue fluid. But since the chlorides easily permeate the membranes of the organism, the chloride concentration of the tissue fluid is probably the same throughout the body and not much different from the concentration in serum. In patients suffering from pleuritis I have determined the chloride concentration 16 times, and always found the same values as in serum.

In consequence of the chlorides being found chiefly in the fluids of the organism, the chloride content of the organs depends much on their water content. The cells of the stomach form perhaps an exception. According to Rosemann, the cells of the stomach have a special affinity for chlorides, for which reason they can store chlorides between the periods of secretion, so that the chloride content of the fasting stomach is higher than that of the blood. Apart from this the chloride concentration in the organs is approximately proportional to their water content. In recent years the chloride content of the organs has

been examined by several investigators, as a result of which it has been found that the chloride concentration varies between 0.1 and 0.4 per cent. The greatest concentration has been found in the lungs and in the skin, which according to Wahlgren contain ⅓ of all the chlorides of the body. On the other hand, on a salt poor diet the chloride output is chiefly due to the skin, while other organs do not lose any salts.

The amount of chlorides with which the body is supplied varies a great deal in proportion as salt is added to the food. It has long been known that some nations use much salt in their food, while others do not use salt at all. Sallust tells us that the Numides despised salt, and Plutarch was astonished to find that the priests in Egypt did not salt their food. Widal and Javal point out that the tribes still leading a nomadic life do not use salt, and that they begin to do so only when they settle and follow agricultural pursuits. Also many other authors point out that vegetarians, on the average, use more salt than meat eaters. According to the theory of Bunge the reason is that vegetables contain mainly K salts, especially potassium carbonate, which reacts in the organism with sodium chloride, forming sodium carbonate and potassium chloride. The carbonate is excreted, while the potassium chloride is retained and substitutes the sodium chloride. To compensate for this loss, vegetarians are disposed to salt their food. This theory of Bunge is denied by several authors. According to Forel, a sect of vegetarians, living at Locarno, do not use salt at all. Some herbivorous animals, for instance the hare and the rabbit, do not eat salt. Widal therefore agrees with Lapique, that vegetarians use salt simply to impart a greater flavor to their diet.

Although the chloride content in the diet varies, not only with the individual, but also with the nation, some authors have nevertheless tried to calculate the average intake of chlorides in the diet. Dastre estimates that Europeans, on the average, have about 17 gm. sodium chloride in their diet per day. Laache estimates 10-15 gms. for Norwegians.

It has long been a well-known fact that the salt in the food is mainly due to the use of salt as a condiment and as a food preserver. The amount of chlorides we get in our food does not therefore correspond to the amount necessary for the organism.

Sodium chloride is common in nature, and all our foodstuffs contain some chloride. The need of the organism is therefore always satisfied by the chlorides which the foodstuffs contain. Dastre pointed out that neither animals nor human beings can be put on their chloride minimum without the salt of the food being extracted.

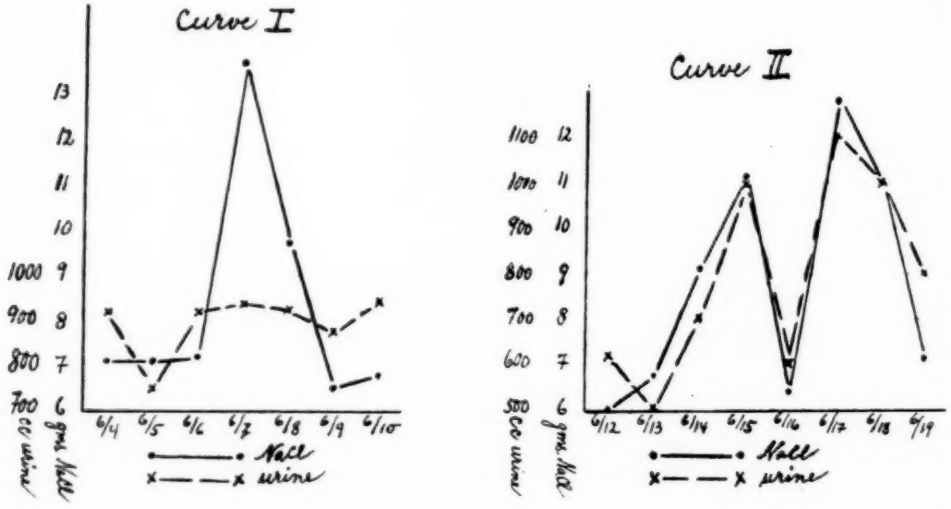
The chloride minimum for human beings has not yet been determined with certainty. During inanition the chloride output decreases rapidly in the first few days, later on it diminishes slowly. Luciani found in Succi from the fourth to the thirtieth day of inanition an average daily output of 0.66 gm.

The output during inanition does not, however, represent the need of the organism. Bunge is of the opinion that the organism needs one or two grams of chlorides per day on ordinary diet, and Mayer has shown by experiments made on himself, that it is possible to live and feel well on 1.25 gm. per day, at least for some weeks.

The chlorides are excreted mainly through the kidneys. A small portion is excreted through the skin and the intestines. In healthy persons the excretion from the skin and the intestines is so small that it need not be taken into consideration in examination of the metabolism. In case of diarrhea, however, the excretion from the intestines may increase a great deal. Javal found in a patient suffering from nephritis and diarrhea an excretion of 9.51 gm. chlorides in the feces in 24 hours.

Under physiologic conditions the chlorides are excreted rapidly, provided that the intake does not surpass a certain upper limit; 10 to 15 gm. chlorides are as a rule excreted in two or three days. Even a much greater amount of chlorides can be excreted in a short time. Lemierre and Digne found in a patient with hysteric polyuria an excretion of 80 gm. in twenty-four hours.

To determine the power of chloride excretion of the kidneys the organism must be in chloride balance. An exact equilibrium cannot be obtained and it cannot therefore exactly be determined when the surplus of chlorides is excreted.

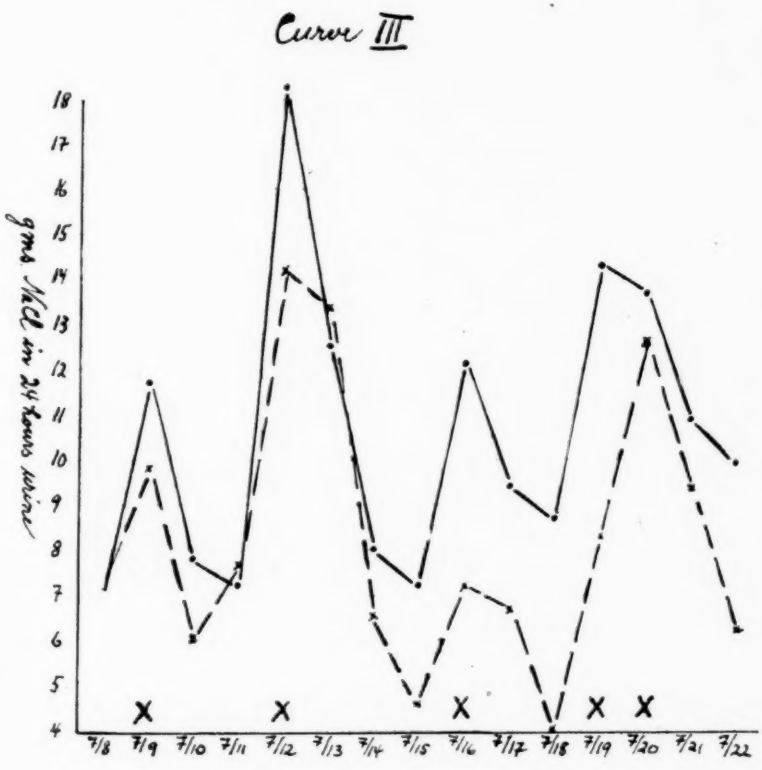


The water content of the organism is of importance for the excretion of the chlorides, because the power of concentration of the kidneys may vary even under physiologic conditions. Some people may excrete the surplus of chlorides without an increase of the diuresis, while others get an increased output of water, so the concentration of the urine does not change. The chloride output is then, as a rule, small on the first day; but if a great portion of water is taken together with the chlorides, the salt is excreted much faster.

Curve I demonstrates the former type of chloride excretion. The person experimented on was a convalescent, whose urine was normal. He lived on a constant diet, containing about 7 gm. chlorides. As will be seen from the curve, the majority of the 10 gm. added are excreted on the first day, the rest being excreted the following day. The diuresis is practically unchanged.

Curve II demonstrates the latter type of excretion. The person experi-

mented on suffered from slight rheumatic pains without any objective findings. The urine was negative. The diet was the same as in the case of the first person. As will be seen, the curves for the excretion of water and chlorides are almost parallel, and the excretion of chlorides reaches its maximum on the second day. When the experiment is repeated in such a way the 1000 c.c. water is given with the salt, the greater part of the salt is excreted on the first day. On account of his small power of concentration this individual cannot excrete the chlorides as fast as the former person, unless a fair amount of water is given with the salt. It is often seen that the concentration power of the kidneys increases when greater amounts of salt are added to the diet for some



time. The concentration of the chlorides will, however, never surpass a certain upper limit, which Ambard has found to be 2.2 per cent.

As will be seen, the organism rapidly excretes the surplus of salt, provided that this surplus does not surpass a certain upper limit, and, consequently the chloride excretion will be proportional to the intake of chlorides. I have examined the chloride excretion in two persons, living on ordinary hospital diet. As will be seen from the curves, the excretion varies considerably from day to day, viz., from about 4 to about 18 gm. The days on which salt flesh or salt fish are given are marked "X" on the curve, and it will be observed that the excretion of chlorides is much greater on the "salt days" than on the other days.

THE PATHOLOGY OF CHLORIDE METABOLISM

It has long been recognized that concentrated solutions of chlorides, or chlorides in substances taken per os, act toxically, owing to the irritation on the stomach and the intestines. Of late years some authors, for instance Finkelstein and Schaps, have emphasized that even dilute solutions, especially when used intravenously or subcutaneously, act toxically, producing the so-called "salt-fever," which was supposed to be due to influence on the temperature centre. Several other authors, among them Jorgensen, have however never got increased temperature when fresh distilled water was used for the injections, while increased temperature often happened when the distilled water had been kept for some time. These authors therefore are of the opinion that the "salt fever" is due to bacteria. These experiments coupled with our experience of the "salvarsan fever," which is now generally looked upon as bacterial in origin, makes it probable that salt fever also is due to bacterial products.

As far as we know, the chlorides do not alter their constitution during their passage in the organism. The changes we know in the chloride metabolism are therefore only of a quantitative nature, consisting of a diminished or an increased amount of chlorides in the organism.

Diminution of the chlorides of the organism is little known and is obviously not of great importance. French authors, for instance Mestrezat, emphasize that the chlorides in the cerebrospinal fluid are diminished in tuberculous meningitis. I have confirmed this in two cases. In 7 patients suffering from nontuberculous diseases I found the concentration of the chlorides between 0.68 and 0.72 per cent, while in two cases of tuberculous meningitis the concentration was 0.59 and 0.61 per cent, respectively.

Far better known and investigated is the increased concentration of chlorides in the organism.

Increased concentration due to increased intake, which Widal and Javal have produced, is of no pathologic interest. All other kinds of increased concentration are due to *retention.*

The retention may be a direct one, due to retention of molecular chloride, of –Cl, or of the cations with which –Cl forms salts, especially +Na, or the retention may be an indirect one, due to retention of water. Owing to the osmotic pressure a retention of water is followed by a retention of chlorides.

A retention of molecular chlorides is possible only when the molecules are adsorbed to the tissue or circulating protein, the dissolved chlorides being nearly all dissociated. The theory on the "adsorbed chlorine" which is due to French authors (Marie, Ambard, Beaujard), is not yet proved. The theory is to explain the so-called "'dry retention." It has been known for a long time that patients suffering from nephritis often retain much chlorine without corresponding amounts of water. René Marie has published a case in which 158 gm. of chlorides were retained and only 7.8 liters water, that is, a retention of about 2 per cent salt solution. Such a retention seems inconsistent with a constant osmotic pressure, unless some part of the chlorides was adsorbed. It must be remembered that the determination of the water retention is difficult, the patient in question often being in a state of inanition. Of importance is also the fact

that small variations of the osmotic pressure may happen, and further that the pressure does not increase proportionally to the retained chlorides, because the dissociation decreases, and finally, that the organism may diminish its content of other electrolytes.

A chloride retention may be due to a retention of –Cl or +Na, or of both ions. Most authors have not determined to which ion the retention is due. Salkowski has, however, found a pronounced Na-retention in pneumonia, and v. Wyss has published a case of nephritis with edema, in which the edema was due to a retention of Na. The patient was cured when he received hydrochloric acid. A secondary retention of –Cl may be due to sodium bicarbonate, which Widal and Lemierre have found in diabetes, and which v.Wyss has demonstated in healthy persons. –Cl is then, according to v. Wyss, retained to neutralize +Na, while Widal supposes that the bicarbonate diminishes the permeability of the kidneys to chlorine. This is made probable by the fact that magnesium sulphate (Widal) and sodium phosphate (L. A. Meyer) may produce retention of –Cl.

The primary retention of water is little known. In many pathologic conditions water is retained, but chlorides are retained at the same time, so that it is difficult to decide which is retained first.

An increase of the chloride content of the organism may be found in several pathologic conditions, the principal of which are:

1. Fever.
2. Decompensation of the heart.
3. Anemia and cachexia.
4. Nephritis.

In fever Redlenbacher found as early as the middle of the last century a pronounced diminution of the chloride output, which on cessation of the fever was followed by an increase. This was confirmed by many authors, among them Röman who found a diminished output in spite of abundant supply. The diminished output is accordingly not due to diminished intake, but to a retention, which is parallel to the water retention. In pneumonia the chloride retention is well known, but where the chlorides are accumulated is not yet known, the chloride content of the exudate being too small to account for the retained chlorides.

The cause of the chloride retention in fever is not yet known. A retention due to the kidneys is often difficult to exclude. Many years ago v. Leyden stated that a chloride retention might exist without any focal infection. The "general influence" of the fever is therefore looked upon as the cause of the chloride retention.

In decompensation of the heart the cause of the retention is due to stasis and edema.

In cachexia, for instance in cancer, several authors, among them v. Müller and Bohne believe they have found a diminution of the chloride output. The investigations of Gärtig and especially of Laudenheimer have, however, shown that there is no special relation between cancer and chloride metabolism. In most cases the diminished output is due to diminished intake of food. In other cases the cause is edema and transudates.

In addition to cancer some authors such as v. Limbeck and Biernacki have found an increased concentration of the chlorides in the blood in chlorosis and anemia.

TABLE 1

NAME	AGE	DIAGNOSIS	CHLORIDE CONCENTRATION IN BLOOD (AND SERUM). DUPLICATE ESTIMATIONS. PER CENT.					
O.A.	25	Anemia	5/17	0.54	0.53	5/19	0.54	0.54
M.S.		Sec. anemia (post. hemorrh.)	6/26	0.54	0.54	6/27 (serum:	0.56	0.55 0.60 0.61)
G.O.		Anemia pernic.	7/11	0.58	0.58	7/15	0.59	0.59
I.G.	30	Anemia.	7/22	0.61	0.61	7/23	0.57	0.58
S.	50	Anemia pern.	9/11	0.56	0.57	(serum	0.62	0.63)
L.S.	15	Sec. anemia.	9/12	0.54	0.55	(serum	0.60	0.60)
R.		Sec. anemia. (post. hemorrh.)	9/12	0.54	0.55	(serum	0.62	0.63)
L.	56	Sec. anemia. (cencer vent.)	7/17	0.53	0.55			
S.		Sec. anemia. (cancer vent.)	7/22	0.55	(serum: 0.66		0.60)	

In several patients suffering from cancer and from primary and secondary anemia I have examined the chloride concentration in blood and in serum (see Table 1).

As mentioned above I have found the normal chloride concentration in the blood between 0.44 and 0.48 per cent and in the serum between 0.55 and 0.60 per cent, that is, the concentration in the serum is about 0.1 per cent greater than in the whole blood. As is evident from Table 1 I have found the chloride concentration of the blood in cancer and in anemia greater, in some cases much greater than the normal, while the concentration in the serum is about normal or only slightly increased. It appears from this that the increased concentration in the blood is not due to retention, but chiefly to the anemia, which has reduced the formed, relatively chlorine-poor elements in relation to the blood fluid.

Since Böhme, toward the close of the "nineties," demonstrated chloride retention in several pathologic conditions, among them uremia, the relation between the *chloride retention and nephritis* has been the subject of many investigations.

Since the experimental studies on animals by Heineke and Meyerstein, as well as by Schlayer and Takayasu, and the clinical and pathologicoanatomic investigations, especially by v. Monakow, it is taken for granted that the nitrogenous products are excreted through the glomeruli, while chlorides and water are excreted through the tubuli. In some of v. Monakow's cases, where the glomeruli were much degenerated, the chloride output was normal, while the N-excretion was much diminished. On the other hand, in cases where the tubuli were affected, the N-excretion was normal, while the chloride excretion was decreased.

It is in cases where the pathologic process is in the tubuli, the pure and the combined nephrosis (Volhard and Fahr) that we find anomalies in the chloride metabolism, while in pure nephritis the chloride output is normal. Most cases of acute glomerulonephritis are, however, in the beginning combined with neph-

rosis; in other words, the process is at first diffuse, later on confined to the glomeruli.

The chloride retention in nephritis may be due to the *kidneys*, the *peripheral vessels* or the *tissue*.

The experiments by Schlayer and Schmid have demonstrated that the kidneys, at least in experimental nephritis, may bar the chloride excretion: in nephritis, due to intoxication with chromium, blood containing increased amounts of chlorides circulates in the kidneys without the chlorides being excreted. In human beings conditions are not so clear. Widal and Javal emphasize that the chloride retention in nephritis is mainly due to the kidneys. On the other hand other authors, as Achard and Ribot, point out that the chloride retention may be independent of the kidneys.

I have examined the chloride content of blood and urine in 9 patients suffering from acute nephritis. All the 9 patients had been taken ill suddenly. They had cephalalgia, edema, increased blood pressure, retention of urea in serum and had protein, blood and casts in the urine. All these 9 cases were typical of glomerulonephritis. In the present paper I shall report in detail only the experiments with 3 patients.

CASE 1.—J. H. Seaman, nineteen years old. The patient was taken suddenly ill a few days before admission to the hospital, with weakness, dyspnea, and edema.

Status on admission to the hospital: Puffiness of the face, edema in the sacrolumbar region and in the lower extremities. Systolic blood pressure 145. Urine: albumin, casts and red and white corpuscles. Urea in serum: 0.065 per cent.

Diet: 1000 c.c. milk, 200 gm. bread and 100 gm. butter. This diet contained about 7 gm. salt.

TABLE 2

DATE	WEIGHT	DIURESIS	NaCl in: 24 HOURS URINE	NaCl in: BLOOD %	
6/6	74.9	730	6.50	0.54	Blood pressure 140
6/7	74.3	905	6.66	0.53	
6/8	74.0	730	4.30		
6/9	73.6	850	3.91	0.53	Blood pressure 125
6/10	73.7	1000	4.70		
6/11	73.3	1400	3.67	0.51	
6/12	73.3	1350	6.21	0.52	
6/13	72.0	1000	6.36		
6/14	70.3	1400	10.64	0.58	+5 gm. salt in 500 c.c. water.
6/15	69.7	1300	10.70		
6/16	68.3	1400	12.00	0.52	
6/17	68.0	1500	12.53		
6/18	66.5	2000	13.40	0.50	
6/19	65.0	2200	14.04		
6/20	64.9	2100	16.88	0.45	
6/21	64.2	2200	14.30	0.45	

This patient, who lived on a constant diet, containing about 7 gm. salt, retained some chlorides during the first week, but on the day the patient was given 5 gm. salt in addition to the diet, the chloride output increased and continued to be high until the edema disappeared about three weeks later. The chloride concentration in the blood, as will be observed, was greater than normal,

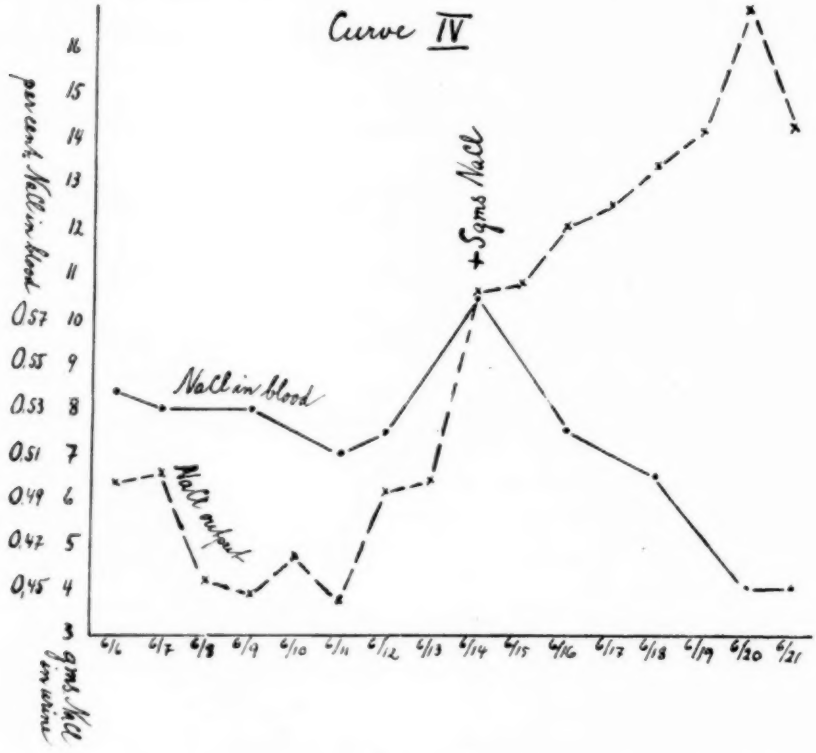
between 0.51 and 0.54 per cent, during the first week. On the day 5 gm. salt were given, the concentration in the blood increased and 6 days later the chloride content of the blood was normal.

CASE 2.—A. S., working man, sixty-one years old. Six days before admission to the hospital he suddenly experienced weakness and dizziness. In the evening of the same day he developed edema in the lower extremities, the day after also in the face.

When he came to the hospital he had edema in the extremities, in the sacrolumbar region and in the face. Some râles in the lungs; temperature normal; urine: albumin and casts; systolic blood pressure 175; urea in serum 0.13 per cent.

Diet: 1000 c.c. milk, 200 gm. bread and 100 gm. butter, containing about 7 gm. chlorides.

The chloride metabolism of this patient was similar to that of the first patient. In the first six days he retained some chlorides, but suddenly, in this case



the day after he got 10 gm. salt, the chloride output rose and was much increased until the edema was gone. The concentration of the blood chlorides was much the same as in the first patient. The first days the concentration was 0.55-0.56 per cent, reached its maximum coincident with the rise in the chloride output, after which it decreased and reached its normal value in the course of five to six days.

CASE 3.—A. B., female, thirty-nine years old. Twelve days before entering the hospital she was suddenly taken ill of cephalalgia, nausea and edema in the lower extremities. On the day of admission she was pale, had some râles in the lungs and edema in the legs. In the urine was found albumin, blood and casts. She was put on a diet consisting of 1500 c.c. milk, 100 gm. bread and 50 gm. butter, containing about 5 gm. chlorides.

In this patient we find the same conditions as in the two previous ones. The chloride output was, however, already going on when the examination began. The curve and the table therefore only show how the chloride output decreased until the edema was gone, when the output corresponds to the intake. At the same time the chloride concentration in the blood fell to the normal value.

Of the remaining 6 patients suffering from nephritis whose chloride metabolism I have examined, I will report on one case later. None of the five was cured during the stay in the hospital. Four of the patients had protein and

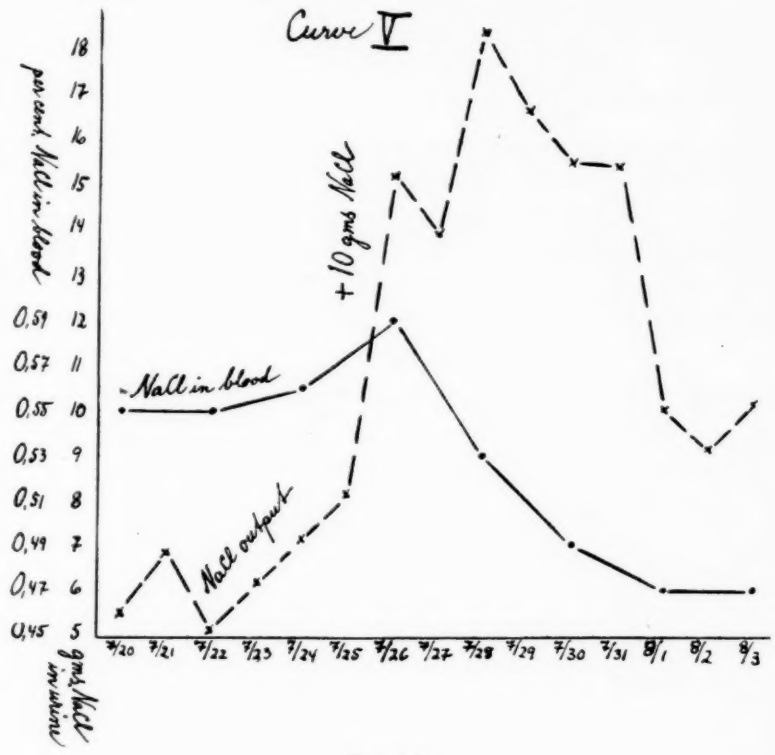


TABLE 3

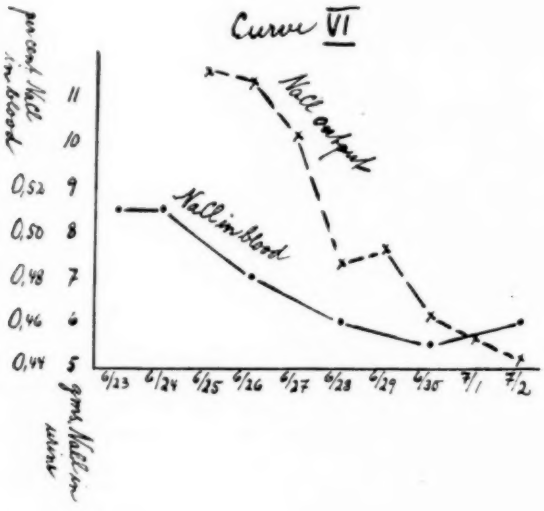
DATE	WEIGHT	DIURESIS	NaCl in: 24 HOURS URINE	NaCl in: BLOOD %	
7/20	71.6	950	5.61	0.55	
7/21		1250	6.75		
7/22		775	5.20	0.55	
7/23	71.5	870	6.25		Blood pressure 180.
7/24		900	7.20	0.56	
7/25		975	8.20		+10 gm. salt in 500 c.c. water.
7/26		1200	15.22	0.59	NaCl in serum 0.67%.
7/27	71.3	1475	13.87		
7/28	70.9	1600	18.62	0.53	NaCl in serum 0.63%.
7/29	69.9	2600	16.64		
7/30	67.2	1900	15.50	0.49	NaCl in serum 0.60%. Blood pressure 170.
7/31	66.6	2000	15.40		
8/1	65.0	1400	10.08	0.47	
8/2	64.0	1300	9.18		Blood pressure 150.
8/3	63.6	1200	10.20	0.47	

TABLE 4

DATE	WEIGHT	DIURESIS	NaCl in: 24 HOURS URINE	NaCl in: BLOOD %	
6/23				0.51	
6/24				0.51	
6/25	61.5	1350	11.61		Blood pressure 155.
6/26	60.1	1500	11.40	0.48	
6/27	58.5	1500	10.20		Blood pressure 155.
6/28	57.3	1100	7.35	0.46	
6/29	56.8	1100	7.62		Blood pressure 140.
6/30	55.9	1175	6.23	0.46	
7/1	55.6	900	5.50		Blood pressure 120.
7/2	55.2	1100	5.20	0.46	

blood in the urine more than four to five months. In these patients the edema disappeared, but in all the chloride concentration of the blood kept higher than the normal, between 0.51 and 0.56 per cent, and the chloride output was delayed.

In contrast to the increased chloride concentration in anemia and cachexia, the chlorides in nephritis are increased both in blood and in serum. The concentration in serum in nephritis I have found between 0.60 and 0.68 per cent.



Summing up the results of these examinations it is evident that the chloride concentration in the blood in 9 patients suffering from nephritis with and without edema is high, while at the same time the chloride output is incomplete. In 3 of the patients the output suddenly rises and continues to be great until the retained chlorides and water are excreted and at the same time the chloride concentration in the blood falls to the normal value. There can accordingly be no doubt that the cause of the chloride retention in these cases of nephritis is mainly to be found in the kidneys, which to a certain extent bar the way for the chlorides. When this barrier gives way more or less suddenly, the retained chlorides and water rush out.

In two of the patients the chloride excretion began when the patients began 5 and 10 gm. salt, respectively. It is difficult to decide whether there is any relation of cause or not. Mohr has several times seen that retained chlorides have been excreted when the patients have received a single fairly large dose of salt.

When the chloride retention is caused by lesions of the peripheral vessels, we may at least theoretically differentiate between a primary chloride retention, and a retention due to retention of water. Practically speaking it is, however, impossible to distinguish between the primary retention of water and the primary retention of chlorides. The result is in both instances the same: augmentation of the fluid in the tissue, which we call edema, when it is demonstrable clinically.

A special form of retention is that which the French call "preedema" or "postedema," the Germans "latent edema."

CASE 4.—H. B., office clerk, thirty-four years old. The last month before admission he felt weak and had shortness of breath. On entering the hospital he had slight swelling of the feet, which had completely disappeared on the following day. From that day no edema was to be found. In the urine were found protein, casts and blood corpuscles.

Diet: 1½ liters milk, 100 gm. bread and 50 gm. butter, containing about 5 gm. salt.

TABLE 5

DATE	WEIGHT	DIURESIS	NaCl in: 24 HOURS URINE	NaCl in: BLOOD %	
6/11	62.3	2000	19.12	0.52	Blood pressure 185.
6/12		1600	17.60	0.51	Blood pressure 180.
6/13	57.2	1525	14.21		
6/14		925	9.81	0.50	Blood pressure 165.
6/15	57.0	1100	9.50		
6/16		550	6.38		
6/17	53.3	500	4.14	0.45	
6/18	53.2	750	4.75	0.46	
6/19	53.2	700	5.20		
6/20	53.2	675	5.50	0.45	

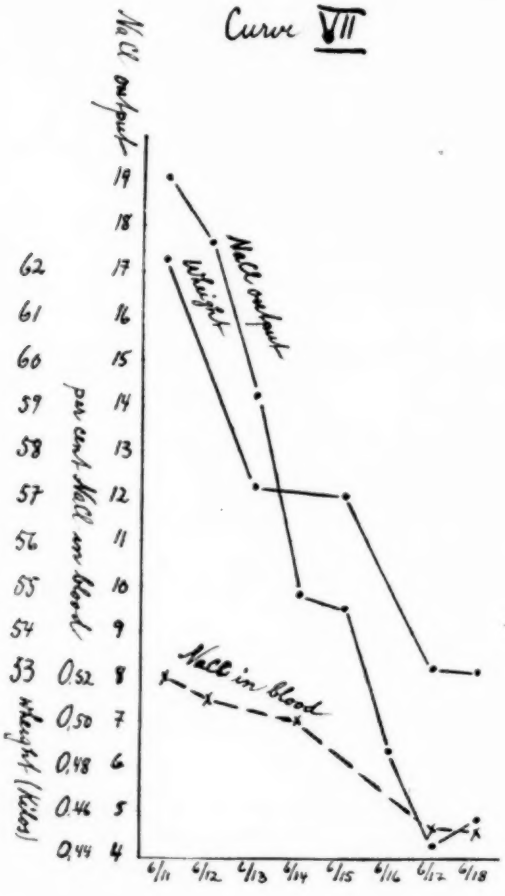
The patient had the usual symptoms of acute hemorrhagic nephritis. The day he came into the hospital he had slight edema of the ankles which disappeared the following day. The day before the examination began he had no edema and no hydrops of the serous cavities. Nevertheless the patient, living on a diet containing about 5 gm. salt, excretes in a week about 55 gm. salt and 9 kilos of water. At the same time the chloride concentration of the blood sinks to the physiologic level, quite in the same way as with the other patients. This relatively large amount of water has accordingly been stored in the deeper parts of the organism and has been demonstrable only by controlling the weight of the patient.

The pathogenesis of edema has been the subject of many investigations. It is not probable that a retention due to the kidneys is sufficient to produce edema. Cohnheim and Lichtheim, transfusing large amounts of water into the vessels, got no edema.

To get edema it is therefore supposed necessary, in addition to the retention from the kidneys or without it, to have a lesion of the peripheral vessels or a pathologic change of the tissue or a combination of both.

In edema, where the retention is supposed to be due to the tissue, the fluid is by some authors thought to be stored intracellularly, by others to be stored extracellularly.

In intracellular retention the colloids of the cells are supposed to have an increased affinity to water due to some intoxication. Iscovesco, who is the inventor of this theory, emphasizes, that it is of great importance for the patho-



genesis of the edema. Fischer, having the same theory, is of the opinion that the increased affinity to water is due to acid intoxication of the tissue. The theory of the edema caused by the colloids of the cells has not gained much credit. The general opinion is that the edema is caused by extracellular retention of water.

Most authors agree that besides the retention due to the kidneys there must be a lesion of the peripheral vessels to produce edema, but opinions differ much as to the importance of these two causes. While some authors look upon the chloride retention as the main cause of the edema (Widal, Strauss and others),

others attach less value to this retention, or look upon it as a consequence of the edema, while the affection of the peripheral vessels is considered of the greatest importance to the pathogenesis of the edema (Albu, Richter a.o.).

Cohnheim, who first pointed out the importance of the extrarenal factors, supposed that the cause was inflammation in the vessels in the skin and in the muscles, which produced an increase of the exudation from the capillaries to the tissue. Heineke and v. Monakow found that the chloride concentration in edema was greater than in serum. This, they find, favors the belief that the edema is due to an active secretion from the vessels.

A greater concentration of chlorides in the edema than in serum does not prove a secretion from the vessels. When the vessels get more permeable, the smallest molecules, especially the chlorides, will of course, first pass through the wall of the vessel, so that also passive transudation may explain an increased concentration in edema. That protein with its big molecules has a concentration of 5-7 per cent, while the concentration in edema only is about ½ per cent goes to prove the same theory.

Senator, and later Schlayer and Hedinger, have extended the theory of Cohnheim to the effect that first the lesion is localized in the vessels of the kidneys, later on in the peripheral vessels, especially in those of the skin. The cause of this lesion is not known.

The importance of the extrarenal factors has been emphasized especially by the investigations of Achard and Ribot. These authors found that the chloride concentration in the blood in several patients suffering from nephritis was not increased, nay, that it was now and then decreased, in spite of the presence of extensive edema. This goes to prove that the chloride retention may be independent of the kidneys.

To sum up, it will be seen that the chloride retention in nephritis appears to belong to two categories:

In the first in which the chloride concentration of the blood is increased, the retention is mainly due to the kidneys, while the extrarenal factors are of minor importance.

In the second in which the chlorides of the blood according to Achard and Ribot are not increased, the cause is entirely or essentially extrarenal, in the capillaries or even in the tissue.

I shall not discuss in detail the clinical applications of chloride metabolism. The edema we find mainly in two types, which evidently correspond to the above-mentioned two types of chloride retention. The edema, which is chiefly due to the kidneys, is, as a rule, extensive, and often disappears rapidly, while the edema which is stable for a long time, is evidently mainly due to other causes than the kidneys.

Opinions differ as to the symptoms of the increased chloride concentration in the blood. Already in 1840 Rilliet and Andral had pointed out that convulsions may arise when the edema is resorbed. Later on, especially Widal and his coworkers reported several symptoms, for instance increased blood pressure, cephalalgia, convulsions, and unconsciousness, which they attributed to the

increased chloride concentration of the blood. It is probable, however, that all these symptoms are not due to the hyperchloremia, but to some other pathologic conditions, which exist along with the increased chloride concentration.

I have determined the chloride concentration of the blood in two patients suffering from uremia, which represented a combination of the "real uremia" and the "eclamptic uremia" (Volhard and Fahr). Both patients had increased urea in the blood, 0.247 and 0.340 per cent respectively. They were somnolent, had a systolic blood pressure above 200 and had convulsions. In one case the chloride concentration in the blood was 0.44 per cent, consequently quite normal, while in the other it was 0.59 per cent, which is the greatest concentration I have found in the blood.

Uremia with increased blood pressure, unconsciousness and convulsions may exist in patients with normal chloride concentration as well as in patients with much increased chloride concentration, which does not go to prove any relation between the chloride concentration and the above mentioned symptoms.

As to the *therapy* of chloride metabolism, Toulouse and Ritchet emphasized in the latter part of the 19th century the importance of limiting the quantity of salt in diet in cases of epilepsy, but salt-poor diet cure did not become general in the clinic until Strauss, some years later, pointed out the significance of the chlorides for the renal and cardiac edema, and Widal and Javal demonstrated in the same period the importance of the chlorides for the edema and the albuminuria in nephritis. Besides in kidney and in cardiac diseases the restriction of chlorides is of importance in some other diseases, for instance, in cirrhosis of the liver (Finsen) and in diabetes insipidus (Tallquist and Erich Meyer). But the salt-poor diet is not of equal significance in all cases of nephritis. In some cases the addition of chlorides seems to remove the edema, while, on the other hand, the salt-poor diet often does not influence it at all. As a rule, the addition of salt will, however, increase the edema, while the edema often disappears when the chlorides of the diet are restricted, which Widal, in particular, has demonstrated.

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BLOOD SUGAR TOLERANCE AS AN INDEX IN THE EARLY DIAGNOSIS AND ROENTGEN TREATMENT OF HYPERTHYROIDISM*

By Eric R. Wilson, A.B., Los Angeles, Cal.

THE blood sugar tolerance as an aid in the early diagnosis of hyperthyroidism cannot be minimized, and is most valuable as an index to the degree of toxicity brought about by increased thyroid secretion. This latter fact is forcibly demonstrated by the return to normal of the blood sugar tolerance in individuals showing an abnomal curve after series of roentgen ray teatments.

TECHNIC OF BLOOD SUGAR TOLERANCE TEST

Patient having fasted the night before was weighed and a sample of blood taken for the determination of the initial blood sugar at 9 A.M. The patient was then given 1.75 grams per kilo body weight of glucose in from 250 to 350 c.c. of distilled water.

The blood sugar was determined by the Lewis-Benedict method. Fehling's solution was used in determining the sugar in the urine.

The physical findings of the five patients coming under our observation and upon which this report is based, were similar in all cases, some being slightly more pronounced in one case than in the others.

All were unmarried women between the ages of 23 and 33.

	BEFORE ROENTGEN THERAPY		AFTER 2 SERIES ROENTGEN TREATMENTS		AFTER COMPLETION 3 SERIES ROENTGEN TREATMENT		
	BLOOD SUGAR TOLERANCE CURVE	SUGAR IN URINE AFTER ADMINISTRATION GLUCOSE	BLOOD SUGAR TOLERANCE CURVE	SUGAR IN URINE AFTER GLUCOSE ADMINISTRATION	BLOOD SUGAR TOLERANCE CURVE	SUGAR IN URINE AFTER GLUCOSE ADMINISTRATION	GENERAL IMPROVEMENT
Case 1	Abnormal	Sugar in 1-1½-2 hr. spec.	Approaching Normal	Neg.	Normal	Neg.	Gen. Improvement marked
Case 2	Abnormal	Sugar in 1-1½-hr. spec.	Approaching Normal	Neg.	Practically Normal	Neg.	Gen. Improvement Fair
Case 3	Abnormal	Sugar in 1½-2 hr. spec.	Approaching Normal	Sugar in 1 hr. spec.	Practically Normal	Neg.	Gen. Improvement marked
Case 4	Abnormal	Sugar in 1½-2 hr. spec.	Approaching Normal	Neg.	Normal	Neg.	Gen. Improvement marked
Case 5	Abnormal	Sugar in 1-1½-2 hr. spec.	Abnormal very slight improvement	Sugar in 1½ 2 hr. spec.	Nearer Normal than previous curve	Neg.	Improvement marked at times Slight gen. improvement

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Distinct lagging of the upper eyelids was noticed at one time or another in all five cases; this sign being slightly more pronounced in cases Nos. 1 and 3.

Case No. 5 was the only one showing a decided exophthalmos.

The thyroid gland was found to be slightly enlarged in all the five cases, this being decidedly pronounced during menstruation; only in one case did we notice a marked hypertrophy of the gland existing continually.

Tremor of the hands was occasionally found to be absent. We found this sign largely dependent upon the degree of irritability and general feeling of well-being of the patient as to whether it became pronounced, absent or only slight in character.

Warm and moist hands was a sign constant in all cases.

The pulse rate was repeatedly taken and in all cases prior to the time of roentgen treatment was found to be above 110 beats per minute. There was usually a marked increase over this found, under the slightest excitement.

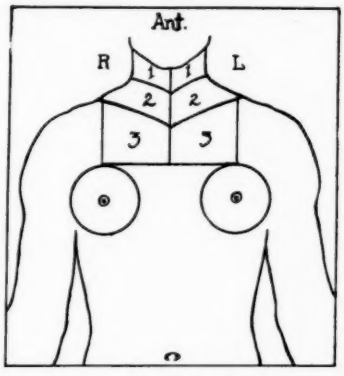

Fig. 1.

The apex beat was found to be forceful in all cases, but only in one was it found to be slightly displaced. The carotids were noted to beat violently under the least excitement, and only occasionally could a blowing murmur be heard over the base of the heart in one or two cases.

The subjective symptoms were in all cases very similar in that there was a general feeling of muscular weakness, lack of "pep," easily tired on exertion, shortness of breath, and occasional palpitation.

All cases gave histories of disturbed menstrual function.

TECHNIC OF ROENTGEN THERAPY (ADMINISTERED UNDER THE DIRECTION OF F. W. HOWARD TAYLOR, M.D.)

The neck below the hyoid bone is anteriorly divided into six sections as shown in Fig. 1; three to the right and three to the left of the median line. Posteriorly these subdivisions do not extend downward as far as they do anteriorly, and are better divided into two areas on each side of the median line. One of these areas is treated every second day, alternating first on one side and then the other, the same with the areas posteriorly which are not treated until the anterior portion has been gone over once. A ten inch spark gap, 3 mm. aluminum filter, ten

inch skin distance and thirty milliampere-minutes was used on each area. A rest of three weeks was given the patient when these areas anteriorly and posteriorly had been treated as above outlined. This then constituted the first series. A second and third series was given, and in all early cases seemed sufficient to bring the blood sugar tolerance curve back to normal.

COMPARISON OF THE BLOOD SUGAR TOLERANCE CURVE BEFORE AND AFTER X-RAY TREATMENT

As will be noticed in a normal control case the blood sugar after administration of glucose rises rapidly reaching its height in one-half to three-quarters of an hour; descends rather rapidly, approaching the normal fasting level, (or it may remain slightly above this level) between one and a half and two hours (Curve No. 2).

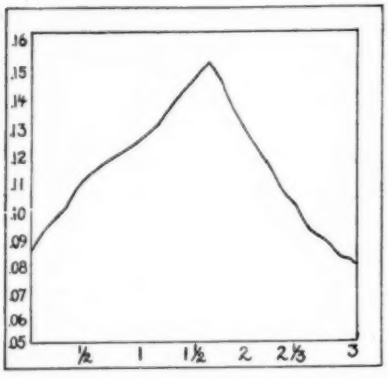

Fig. 2.—Curve No. 1 illustrating typical blood sugar tolerance after ingestion of glucose in case of hyperthyroidism.

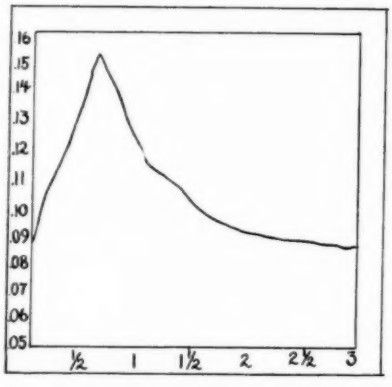

Fig. 3.—Curve No. 2 of blood sugar tolerance after ingestion of glucose. Normal control case.

In cases of hyperthyroidism, the blood sugar rises gradually, reaching its height in one to one and a half hours after the administration of glucose; it falls rapidly and does not reach the fasting level (or slightly above this level) until between two and one-half to three hours after the glucose solution has been administered (Curve No. 1).

The urine gave positive tests for glucose in all cases: this was usually most marked in the one and one-half to two hour specimens after the administration of the glucose solution.

THE COMPARISON OF THE CURVES

Curve No. 1 (Fig. 2), illustrating a typical hyperthyroid curve of the blood sugar tolerance after the ingestion of glucose as outlined in the first part of this article, differs so radically from curve No. 2 (Fig. 3), a typical normal control curve, that no further comment than the above is deemed necessary. Curve No. 3 (Fig. 4) demonstrates a typical blood sugar tolerance curve in a case of hyperthyroidism responding favorably to roentgen therapy after two series of treatments. As will be noted in this latter curve, its tendency is to approach the nor-

mal. In all but one case, after three series of roentgen treatments had been completed, the blood sugar tolerance curve had practically returned to normal. We found that a slight deviation of the curve might exist and it still be considered normal.

The subjective symptoms in all cases showed marked improvement from after the second to the fourth x-ray treatment. The pulse became slower. A decided improvement in muscular weakness was noticed: the return of "pep" was spontaneous, while shortness of breath was greatly relieved. Menstrual function, which had previously been abnormal gradually returned to what had been normal for the individual.

DISCUSSION

In cases of hyperthyroidism the rate of body metabolism is increased, this increase is roughly proportional to the severity of the clinical manifestations. This fact accounts for the clinical symptoms commonly present, such as, loss of weight, warm moist skin and slight elevation of body temperature. The toxic

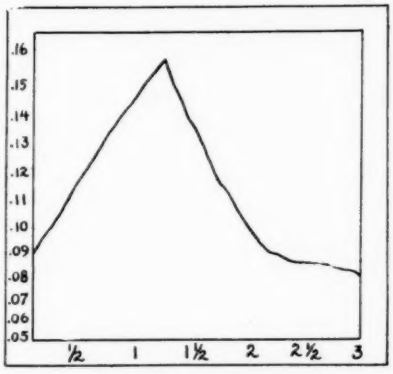

Fig. 4.—Curve No. 3 of blood sugar tolerance after ingestion of glucose in case of hyperthyroidism after 2 series of x-ray treatments.

effect of oversecretion of the thyroid on the cardiovascular system is possibly due to stimulation of the cardiac accelerator nerves. The nervous symptoms are produced by excessive toxic secretion, and the increased irritability and nervousness in turn may tend to greater thyroid secretion, thus establishing a vicious circle. The tolerance for glucose administered by mouth is diminished, which depends on variable factors, namely, the rapidity of absorption from the alimentary tract, or the inability of the body to remove an excess of glucose from the circulation, this is due in larger part to failure of the liver to perform its normal glycogenic function when excessive quantities of sugar are taken by mouth. There may be some influence affecting the threshold limit at which the kidneys begin to excrete the excess of sugar in the urine. It is most probable that all these factors enter into this diminished tolerance for glucose, and particularly the latter in producing the temporary glycosuria. It has been repeatedly demonstrated that there exists an interrelation between the glands of internal secretion, and just as excessive thyroid secretion materially affects ovarian secretion which manifests itself clinically by disturbed menstrual function, so might excessive thyroid secretion cause

marked disturbance of the pancreas in its control over carbohydrate metabolism.

Nevertheless, whatever may be the mechanism directly or indirectly causing this impaired glucose tolerance (the causative factor being the hypersecretion of the thyroid gland), an abnormal glucose tolerance exists early in the disease, making it a diagnostic sign of importance, as well as an index in roentgen therapy.

CONCLUSIONS

The blood sugar tolerance test is of distinct importance in the early diagnosis of hyperthyroidism. That seemingly advanced cases of hyperthyroidism will respond but moderately to roentgen therapy, as shown by the blood sugar tolerance test. An abnormal blood sugar tolerance curve when due to hyperthyroidism will tend to approach the normal under roentgen therapy, indicating that excessive toxic secretion is lessened.

Clinical manifestations of hyperthyroidism may be lessened, but an abnormal blood sugar tolerance curve may exist after series of roentgen treatments.

The blood sugar tolerance curve is an index to thyroid hypersecretion in those cases in which toxic secretion has manifested itself by a decreased glucose tolerance.

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LABORATORY METHODS

NUTRITION EXPERIMENTS WITH RATS. A DESCRIPTION OF METHODS AND TECHNIC*

By Edna L. Ferry**

INTRODUCTION

SEVERAL years ago we published descriptions of the devices and technic employed in our nutrition experiments with white rats.[1] Since then experience and revised plans of study have brought about various improvements in the outfit and methods used. Inasmuch as inquiries received from time to time have indicated that other workers are interested in our experimental methods it has seemed worth while to describe in detail some of their features.

For the successful outcome of feeding experiments the maintenance of hygienic conditions and a supply of healthy stock are essential factors. Where a large number of animals are to be fed it is important to reduce to a minimum the labor involved, and we believe that the apparatus and methods which we have used contribute to this end. In general all parts of cages and food and water containers should be strictly interchangeable so that no time is lost because some one piece does not fit into its proper place.

CAGES

The cylindrical cages (Figs. 1 and 2) used for the experimental animals are 9 inches in diameter and 8 inches high, made of ¼ inch mesh galvanized wire netting, the raw edges being bound with sheet zinc. The cage has no bottom but is set in an ordinary enamel-ware pan with sides 2¾ inches high and about 9½ inches in diameter at the bottom. The sides of the commercially obtainable pans should flare sufficiently to make it possible to stack them compactly for storage. As food containers we use cups of porcelain 2⅞ inches in diameter and 1¾ inches high, such as are attached to bird cages; the water holders are 2 oz. bar glasses (see Fig. 1). In assembling the various parts five or six sheets of paper napkin are introduced into the bottom of the pan to absorb the urine or any water that is spilled. This paper is covered with two discs of ⅛ inch mesh

*From the Laboratory of the Connecticut Agricultural Experiment Station, New Haven, Connecticut.

This paper represents the experience gained in connection with the nutrition investigations conducted by Dr. Thomas B. Osborne and Dr. Lafayette B. Mendel under the auspices of the Carnegie Institution of Washington, D. C., and the Connecticut Agricultural Experiment Station.

**This paper was prepared by Miss Ferry and was nearly ready for the printer when she became seriously ill and died. By her death biological science has lost one of the most promising and enthusiastic of the younger women who are engaged in this field of work. All who were associated with Miss Ferry in the many activities in which she was interested and in which she excelled have experienced a personal loss which they will feel deeply. We ourselves wish to here acknowledge the debt we owe to Miss Ferry for the ability and devotion with which she cooperated with us in the numerous investigations with which during the past decade we have been engaged.—T. B. O. and L. B. M.

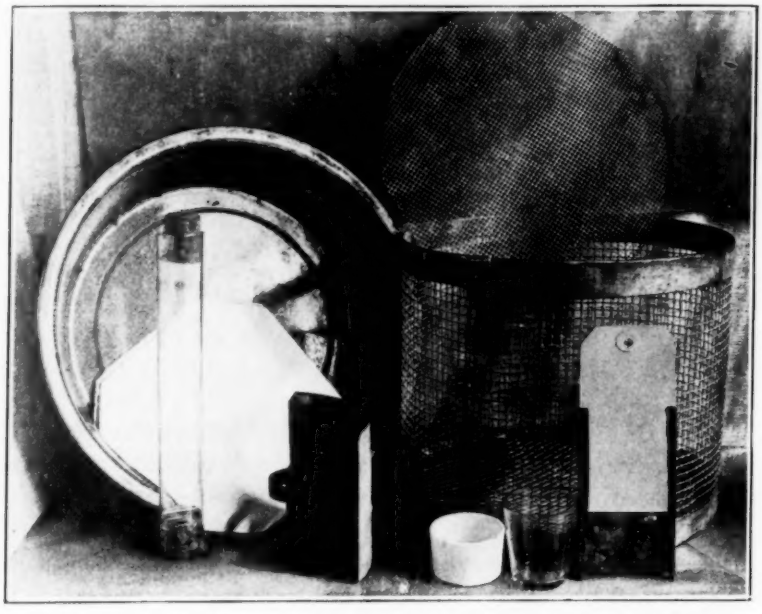

Fig. 1.—Showing the individual parts of the cages and feeding devices used for the experimental animals. The cage and cup holder are made by the Herpich Company, New Haven, Conn. The food cups are obtained from the A. B. Hendryx Co., New Haven, Conn., who also are now prepared to furnish the cages, as well as the accessories illustrated in Figs. 1-6. The netting discs and zinc card holders are cut out in the laboratory.

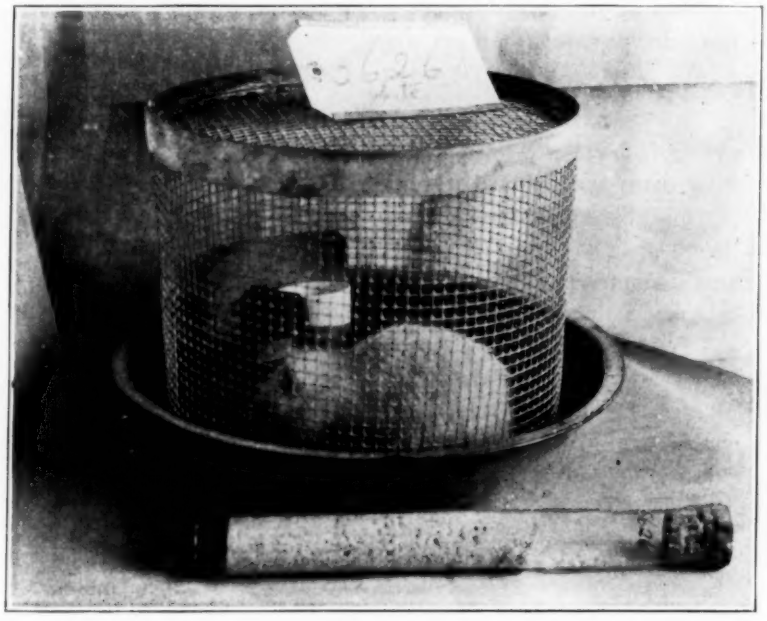

Fig. 2.—Showing the experimental cage in use. The strip on the back of the cup holder hooks over the edge of the pan, thus holding it firmly in position. If a rat acquires the habit of pulling out the glass and spilling the water, a wire hook can be inserted through the back of the holder just above the top of the glass to hold the latter securely.

wire netting to prevent the animals from obtaining access to the sheets. Over the edge of the pan is hooked the specially shaped cupholder (shown in Fig. 1) with food and water containers in place and its bottom resting on the wire disc. The animal can now be placed in the pan and covered with the wire cage.

This arrangement of the cage and its parts presents the following advantages: it simplifies the process of cleaning and it eliminates covers and doors, thus facilitating handling the animals. As the entire cage can be lifted up when the food is placed in the holders, or the rat removed, there is much less danger of being bitten than when the hand must be inserted through a small opening either in the top or the side.

To clean the parts before they are sterilized the cage and cupholder need merely to be rinsed; the wire discs are boiled in water, after which the debris attached to them can easily be removed by rinsing under the faucet. The pans and cups are readily cleaned with a brush. It is our custom to wash and sterilize the cages of the experimental animals with live steam in a large tank twice a week.

Experience has demonstrated that, except for rats with young, "bedding" is unnecessary if the temperature of the environment is suitable. Our rat rooms are usually maintained at a temperature of 65-70° F.

In order to obtain rats of known age and vigor we have found it advantageous to raise our own, and for this purpose a breeding colony of about 200 animals is maintained. These are kept in rectangular cages, 18 inches long, 12 inches wide, and 8 inches high (Figs. 3 and 4). The front and sides of the cage are made of ½ inch mesh galvanized wire netting, reinforced along the top, bottom and corners with strips of zinc. The back and top are made of sheet zinc, the top being attached to the back by hinges which make it possible to open the entire top of the cage. The top is held closed by a small brass catch in front. The bottom of the cage is made of heavy netting with a 1 inch mesh. The cage rests in a galvanized pan 18½ inches long, 12½ inches wide and 1 inch deep. To absorb moisture the bottom of the pan is covered with one or two sheets of thin blotting paper held in place by ⅛ inch mesh wire netting.

These cages are washed under a faucet, using a brush whenever necessary, and are sterilized with steam once a week. Fresh papers are put in the pan twice a week and the sheets of wire netting are boiled to remove the adherent dirt. The coarse netting on the bottom of the cage permits the feces and debris of the food to fall through into the pan when the cage is lifted. This makes it possible to renew the papers and boil the sheet of fine netting as often as may be desirable without handling the rats. In these larger cages the water cups are like those used in parrot cages and are slipped in through an opening in the front of the cage. Usually four rats are kept in one cage. No bedding is used.

Either just before or just after a litter of young is born the mother is removed to a special cage, 9 inches square and 9 inches high (Figs. 5 and 6). This is like the larger ones except that it has no bottom because the very young rats were sometimes crushed on the heavy netting of the large cages. The fine wire netting is left as a separate sheet so that it may be boiled to facilitate cleaning. In these cages water is furnished in a glass drinking tube, inserted through a hole in the top of the cage as shown in Figs. 5 and 6. This prevents the rat

from spilling the water and thus wetting the bedding. Crepe paper strips obtained from the Denison Co. are used for bedding. They have proved much more satisfactory than cotton, because threads of wet cotton may become wound tightly around the legs or tail of a newborn rat and cause the loss of a member. When the young rats are about three weeks old they are transferred with the mother to one of the larger cages to afford them better opportunity for exercise. The mother is left with her young until they are at least four weeks old.

STERILIZATION OF CAGES

The cages are sterilized in a galvanized tank 3′ 6″ long, 2′ 5″ wide, and 2′ 5″ high with hinged top. It holds 12 large breeding cages or 36 round experi-

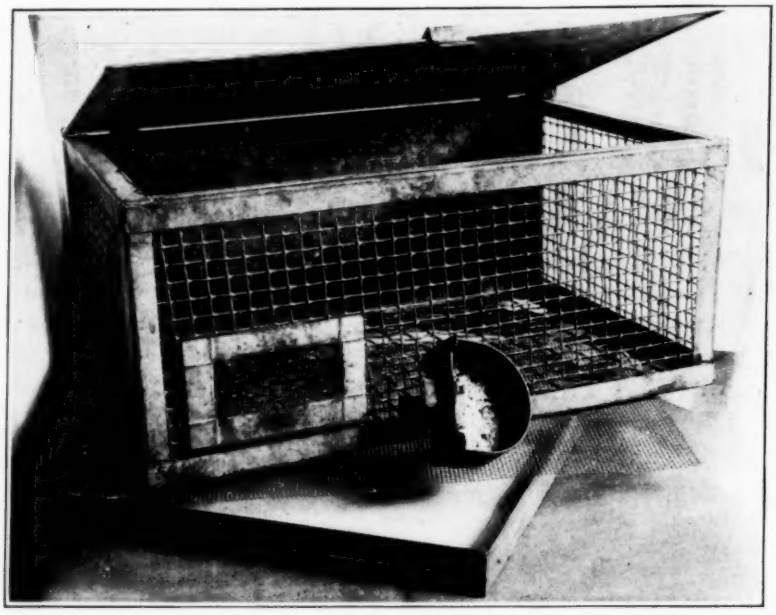

Fig. 3.—Showing the individual parts of the cages used for the animals in the stock colony. The cages and pans are made by the Herpich Company and the water cups are obtained from A. B. Hendryx Company, both of New Haven, Conn.

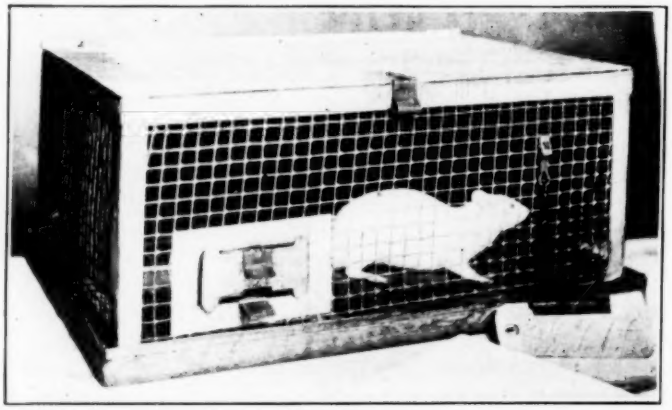

Fig. 4.—Showing the cage of the stock colony in use.

mental cages at once. The steam enters through a pipe at the back of the tank. At one end, near the top is inserted a piece of stove pipe, the free end of which passes to the outside of the building through a window. At the opposite end of the tank, at the bottom, is attached an electric blower or fan. After the steam has been passed into the tank for 10 minutes the current of air is turned on, and the steam blown out of doors before the tank is opened. The escape of large quantities of steam into the room is entirely avoided. A pipe drains the condensed steam away from the tank.

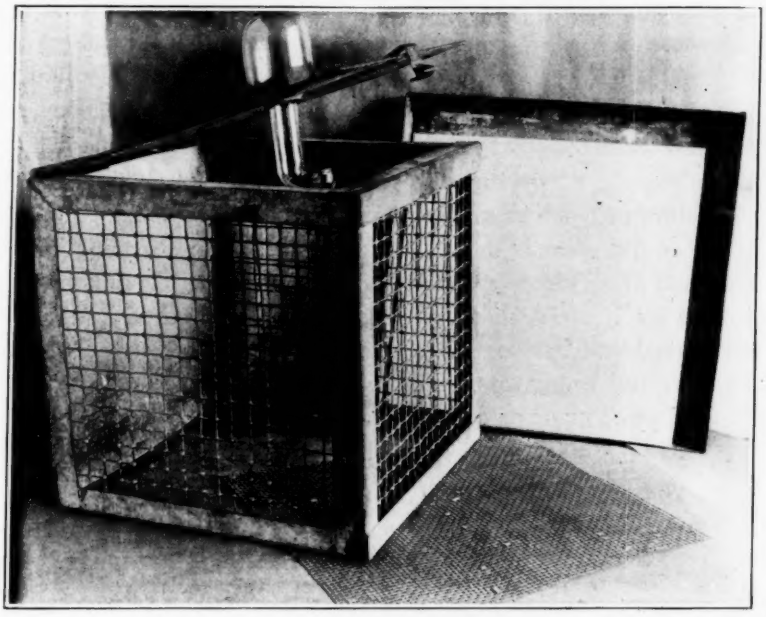

Fig. 5.—Showing the individual parts of the cages used for the breeding females. The cages and pans are made by the Herpich Company, New Haven, Conn., and the water tubes by E. Machlett & Sons, New York.

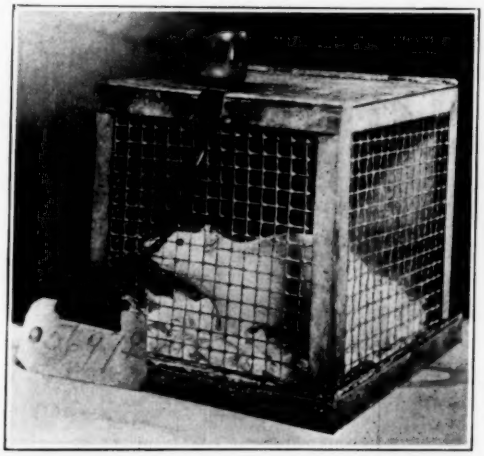

Fig. 6.—Showing the breeding cage in use.

FOOD

The food of the experimental animals is made into a coherent paste which the rats will not scatter. When fat is used, the finely ground protein, carbohydrate and salts are mixed thoroughly, stirred into the melted fat and the entire mixture passed repeatedly through an electric food chopper. Such a water-free food is practically sterile and can be kept for several weeks without any apparent deterioration.

When the foods are to be prepared with water, the dry ingredients are thoroughly mixed, usually by passing them through the food chopper, and enough water is added to each day's ration to make it the proper consistency. Each morning the food which is left over is removed from the food cup and dried in an oven. At the end of the week the daily residues are collected, weighed, and their weight deducted from the total amount of the dry ingredients given to the animals. In the process of drying, the residues lose about 8 to 10 per cent of moisture, but allowance can be made for this in computing the food intakes.

The food of the animals in the stock colony consists of "dogbiscuit" made by the Potter and Wrightington Co., Charles River Ave., Boston, from a formula furnished them by Professor Castle. Once or twice a week these animals are given fresh vegetables of some kind, usually carrots when they can be obtained. Nursing mothers and young rats under four to five weeks of age receive in addition a milk food paste made as follows:

	per cent
Milk powder	60
Starch	12
Lard	28

WEIGHING

The rats are weighed on a spring balance shown in Fig. 7. The dial reads from 0-1000 grams in 5 gram divisions. Although the readings between the 5 gram divisions must be estimated, the errors made during a long experiment are negligible. Where many animals are to be weighed the use of a spring balance saves time.

Food enough for a week or more for each rat is put into a heavy glass tube 10 inches long and 1⅛ inches in diameter with a cork at each end (see Fig. 2). From this tube the food is forced out into the cup as desired, by using one cork as a plunger. At the beginning and end of each weekly period the tube, cup and food in them are weighed on a spring balance (see Fig. 7). The scale on this balance reads from 0-400 grams in 2 gram divisions. The little pan for holding the tube and cup is made of sheet aluminum.

The most satisfactory methods for marking the food tubes and cups of the individual rats are as follows: The number of the animal is written on the tube with indelible ink and then covered with a thin coat of shellac; in the case of the cups, the glazing is removed from a small spot with an emery wheel, the number of the rat is then written on the rough spot with pencil and covered with shellac. The shellac prevents the numbers from being accidentally washed off, but they can be removed easily by soaking in dilute alkali.

GENERAL CONDUCT OF EXPERIMENTS

Each morning the food and water cups are taken out of the cup holders and placed on top of the individual cages. The water glasses are collected, for washing and filling, in large trays with wire netting bottoms. A wheeled table such as is used in hospitals, greatly facilitates distribution of the containers. The food

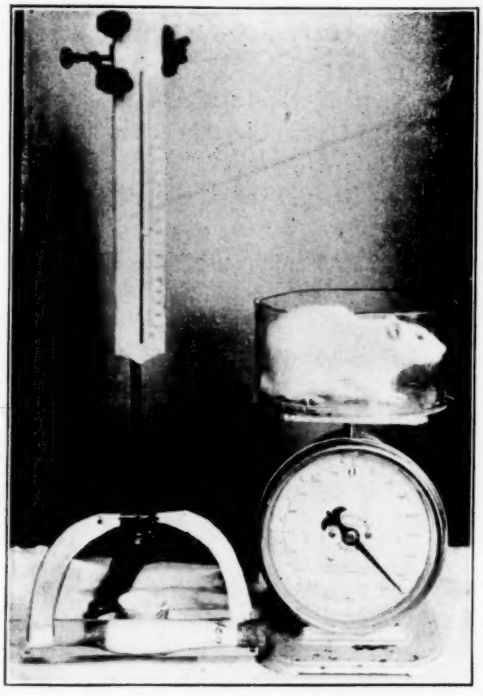

Fig. 7.—Showing the devices used in weighing the food and the rats. The food balances are made by the Chatillon Company, New York. The rat balance was obtained from Chas. Forschner & Sons, New York.

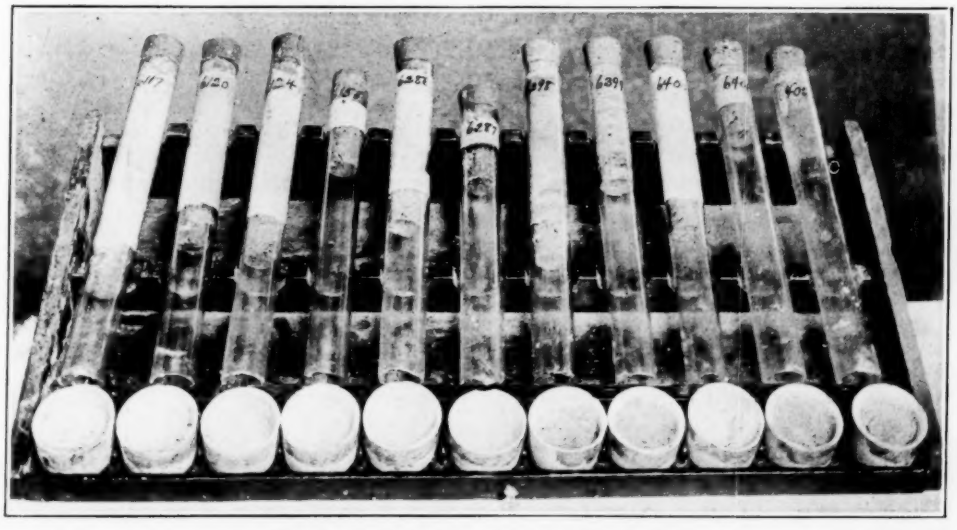

Fig. 8.—Showing tray for food tubes in use.

cups and tubes of those animals whose food is to be weighed are collected in trays (see Fig. 8) and weighed. The remaining food cups are filled without removing them from the tops of the cages, the tubes of food being kept at the left of each cage.

Vitamine or other preparations which are to be fed apart from the basal ration are offered in additional cups introduced into the cages. Recently the use of carefully prepared compressed tablets of these accessory materials has been found most convenient.[2] Formerly small sized scoops were used to measure portions of these products.

At night a strip of board about 4 inches wide is placed along the tops of series of cages to prevent any of the animals from tipping up the latter and escaping.

On Saturday enough food is put into the cups to last until Monday, so that on Sunday it is necessary merely to supply any desired accessory food and water.

By having enough clean cages it is possible for three persons to weigh the animals, chart the weights of the rats, to clean and sterilize the cages at the rate of almost three per minute.

The rats are weighed first when about three weeks old; thereafter the stock rats are weighed once a week and the experimental animals twice a week. The young rats are usually started on experimental diets when they are between 30 and 40 days old and weigh from 50 to 80 grams. Animals weighing decidedly less than the average for their age are never used in diet experiments.

IDENTIFICATION

In the stock room where several animals are kept in each cage the individuals are distinguished by staining patches of their fur with different nonpoisonous colors. By using two colors and marking different parts of the body it is easily possible to identify a dozen or more animals in a single cage.

The cages containing the experimental animals are arranged in numerical order. The color of the correspondingly numbered location sign serves to indicate the days on which each animal and its food are weighed. The number of the rat is printed on a tag which is inserted in a zinc holder placed on the top of the cage. The holder keeps the rat from destroying the tag, and also is heavy enough to prevent the tag from being knocked off accidentally.

BREEDING

In breeding the animals, three females are usually mated with one male, care being taken to select only vigorous individuals and to avoid inbreeding if possible. A female which has successfully raised a litter of young is not remated until three or four weeks after the young are weaned, and she has regained the weight lost during the lactating period. Females more than a year old are discarded for breeding purposes, but males are frequently used until they are nearly two years old.

RECORDS

The records of the experiments are kept in a loose leaf notebook, the pages of which are numbered serially to correspond with the rats. At the top of the

page is recorded the sex, date of birth, and parentage of the animal and the purpose of the experiment. Below are columns for the date, weight of the rat, weight of the food + tube + cup, and amount of food eaten. There is also space for the formula of the ration used and comments on the condition of the animal, or reasons for making any changes in the diet (Fig. 9). To facilitate a rapid survey of the changes in body weight and food intake a corresponding record is kept in the form of graphic charts (see Fig. 10).

RAT 4082.

Parents 3503 ♀ and 3437 ♂
Born Feb. 10, 1917 Female

Diet: Soy cake + starch + lard

Purpose: To study growth on soy cake as the sole source of protein, inorganic salts, water-soluble vitamine and fat-soluble vitamine.

Date 1917	Weight gm.	Tube + cup + food gm.	Food eaten gm.	
Mar. 1	33			
8	48			
14	60	269		Soy cake 37.5%
15	57	266	3	Starch 42.5
				Lard 20.0
15	57	266		
19	58			
22	58	239	27	
22	58	239		
26	61			
29	59	208	31	
29	59	294		
Apr. 2	61			
5	63	262	32	
5	63	262		
9	69			
12	74	209	53	
12	74	303		
16	74			
19	78	250	53	
19	78	233		Food changed to study effect of improving the inorganic salts in the diet.
23	100			
26	110	171	62	Soy cake 37.5%
				Salt mixture 4.5
26	110	253		Starch 38.0
30	121			
May 3	124	185	68	

Fig. 9.—Showing a specimen page from the laboratory notebook.

In addition to these records a card catalogue which gives the ancestry for three or four generations is kept. This is useful as a guide in selecting animals for mating so as to avoid close inbreeding. These cards show not only the ancestry of the individuals but also the progeny resulting from each mating, and in the case of experimental animals a list of the different diets used and the dates between which each was fed, thus giving in tabular form a brief resume of the history of each rat (Fig. 11).

INDEXES

The following indexes have proved very useful:

1. An alphabetical list of the proteins or other food factors which have formed the topics of investigation, together with a numerical list of the rats fed on the corresponding diets.

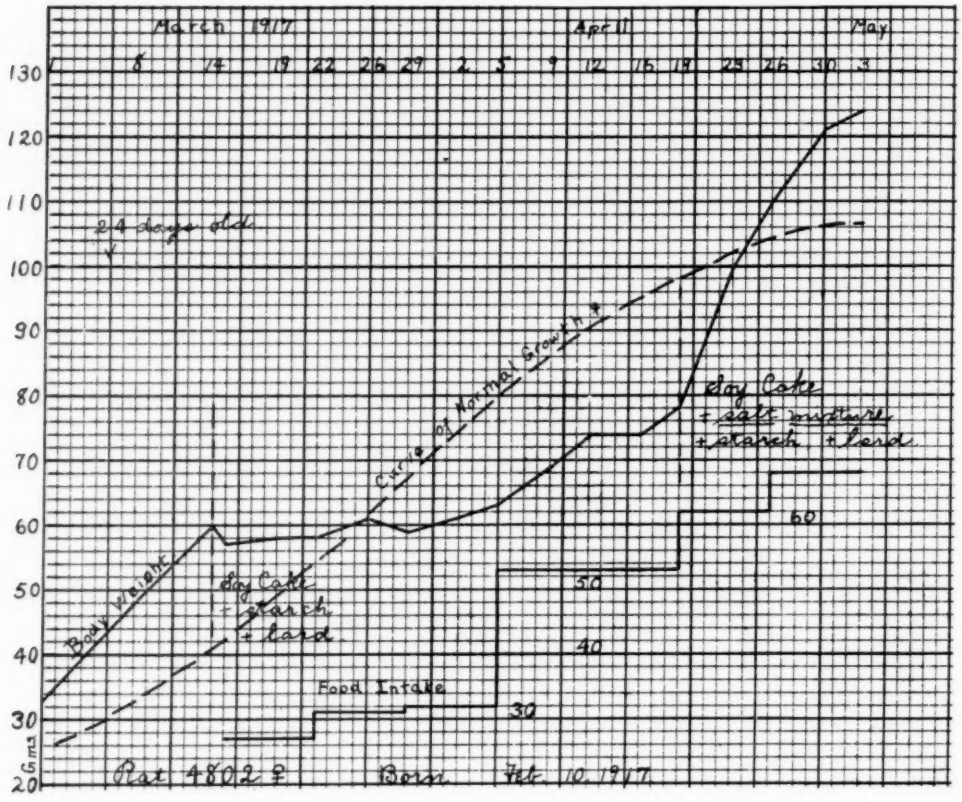

Fig. 10.—Showing a specimen page from the laboratory book of body weight charts.

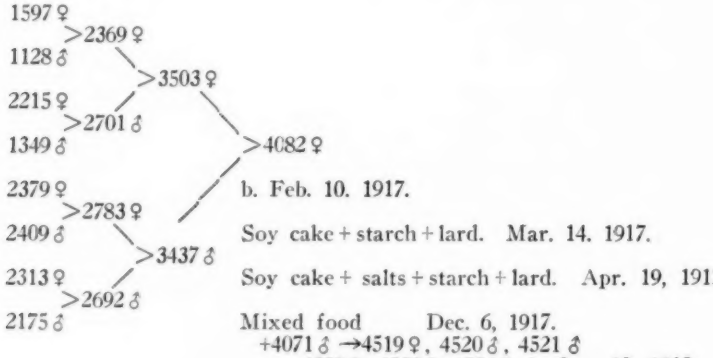

Fig. 11.—Showing a specimen card from the heredity catalogue.

2. A list of the experimental animals classified according to the types of experiments which they represented, such as "growth," "maintenance," "protein minimum," "amino-acids," etc.

3. A chronological, classified record of the new experiments begun, and changes made during each month. This last is chiefly useful when it is desirable to review the work from an historical standpoint. The importance of records of this sort becomes apparent in investigations, such as ours, where several thousand animals have been employed.

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A NEW FORM OF ETHERIZING DEVICE FOR USE IN ANIMAL EXPERIMENTATION*

By G. Raap, A.B., A.M., and D. E. Jackson, Ph.D., M.D., Cincinnati, Ohio

In recent years a number of forms of ether valves, etherizing devices, and artificial respiration machines have been described, among which may be mentioned those by Guthrie,[1] Jackson,[2] Gates,[3] Hoyt,[4] Sollmann[5] and others. In the present article we wish to describe briefly a new form of etherizing apparatus

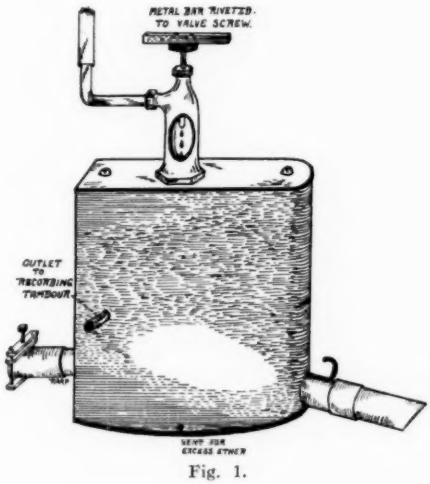

Fig. 1.

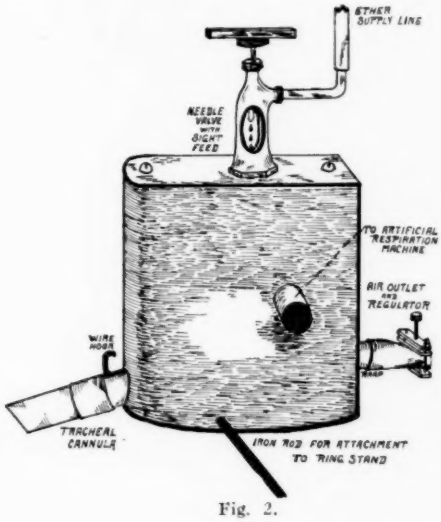

Fig. 2.

which we have recently devised. This apparatus is well adapted for use with all the ordinary types of artificial respiration machines, such as those of Gates,[3] Jackson,[6] Hoyt,[4] Stewart and Rogoff,[7] Meltzer,[8] Hanzlik,[9] Fells[10] and Higgins,[11] or even with an ordinary hand bellows.

*From the Department of Pharmacology, University of Cincinnati Medical School, Cincinnati, Ohio.

As shown in Figs. 1 and 2 the device consists of a brass box held in position as shown in Fig. 3 by a stand and clamp, permitting of adjustment in height from the table according to the size and position of the animal operated on. The box is curved on the bottom to fit the surface of the animals neck and jaws. Fig. 4 shows the box with the top and end removed to illustrate the arrangement of the interior which contains a U-shaped strip of woven wire gauze with four or five layers of ordinary cotton gauze sewed over the outside of it. This serves to give ample evaporation surface and to deflect any currents of air which might otherwise become insufficiently laden with ether vapor. Into one side of the box is soldered a short tube one half inch in diameter, to which the rubber hose from the artificial respiration machine may be attached. The tracheal cannula

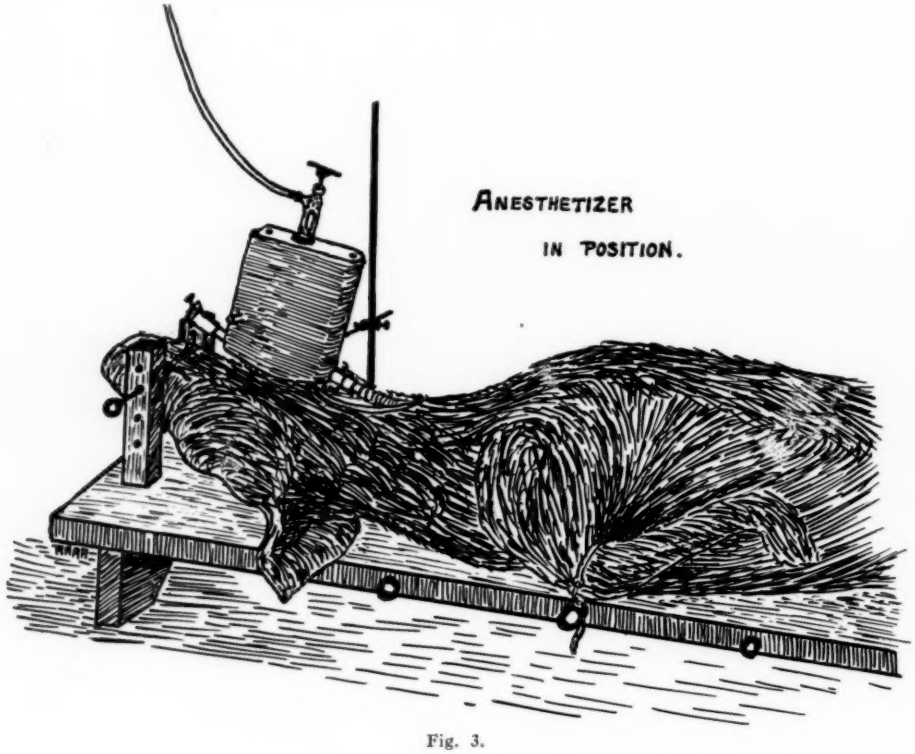

Fig. 3.

is attached to the front of the box, near the bottom and is inclined at a slight angle to facilitate rapid insertion into the incised trachea. To permit of use in animals smaller or larger than the average sized dog, the tracheal cannula is supplied with removable tips which can be attached to suit the animal (including cats).

Into the side of the box nearest the operator is soldered a short piece of one-fourth inch tubing to which the rubber tube leading to the respiratory tambour is attached. A very small hole is made in the bottom of the box near the tracheal cannula opening. This hole permits escape of any pure ether which might accidentally fall to the bottom of the box, thus preventing the ether from getting into the trachea or lungs.

The air outlet and regulator, which, as shown, consists of a short rubber tube supplied with an adjustable screw clamp, is placed opposite the tracheal cannula, and is so situated as to allow the animal a very free air-way through which to breathe. By slightly opening or closing the screw clamp the amplitude of the respiratory tracing (tambour) can instantly be adjusted to any desired height.

Ether is supplied from a reservoir (mercury bulb or aspirator bottle) hung about 12 or 15 inches above the animal and arranged to prevent unnecessary evaporation by means of a small air ingress tube as shown in Fig. 5. A rubber

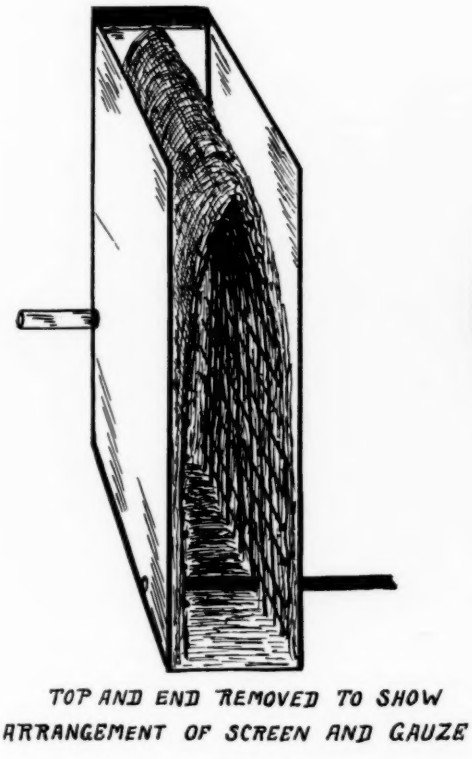

Fig. 4.

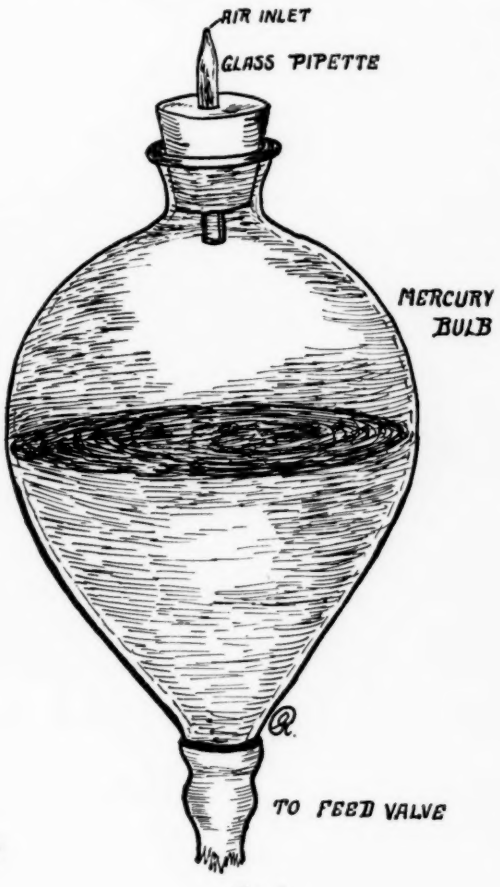

Fig. 5.

tube conducts the ether to a small sight feed needle valve which is soldered into the top of the box. Thus the supply of ether breathed by the animal can be very quickly and accurately regulated by a simple adjustment of the needle valve. This works equally well for either natural or artificial respiration, or if changes are quickly made from one to the other. But if artificial respiration is given, a pinchcock must be placed on the tambour tube to prevent an excess of air being forced from the box into the tambour, thus injuring the rubber membrane over the tambour.

The artificial respiration machine may be attached before the operation is begun and started and stopped at any time by means of an electric switch.

One special advantage secured by attaching the tambour directly to the apparatus is the avoidance of changes in the character and amplitude of the respiratory tracing due to changes from the abdominal to the thoracic type of breathing, or vice versa. These spontaneous changes always affect the character of respiratory tracings obtained by means of a stethograph tied around the chest or abdomen of an animal.

The device has been of great value in open chest work in which cardiac, lung or pulmonary pressure tracings were to be made. This is due to the fact that the rate and extent of lung inflation always remains constant, because there is no change in the dead space of the tubes, etc., through which the air is supplied to the animal, and ether can be given or stopped at any desired moment.

It is advisable to coarsely adjust the needle valve before the experiment is begun. The ether supply tube can then be closed off completely with a pinch cock until the tracheal cannula is inserted. A small wire hook is placed on the tube just above the attachment of the replaceable cannula tip. Around this hook the string used to tie in the cannula tip is fastened, thus preventing the cannula from being pulled out of the trachea.

The device uses less ether to carry on anesthesia than is usually required with an ordinary ether bottle. It is especially useful for students, since the confusion of changing from ether to air or vice versa in case of accidents, etc., is almost entirely eliminated.

The device may be obtained from the Max Wocher & Son Co., 19 West Sixth St., Cincinnati, Ohio.

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EDITORIALS

Major General Gorgas

WILLIAM CRAWFORD GORGAS was born at Mobile, Ala., October 3, 1854. His father, Josiah Gorgas, was born in Pennsylvania in 1818, graduated at the United States Military Academy at West Point in 1841 and was assigned to the Ordnance Corps. He served with credit in the Mexican War with the rank of captain. When the Civil War began he cast his lot with the Confederates and was made head of the Ordnance Department with the rank of Brigadier General. One of the buildings in which General Josiah Gorgas manufactured gun powder, now unoccupied and falling into decay, stands near Macon, Ga. After the Civil War General Josiah Gorgas was elected Vice-Chancellor of the University of the South and later became President of the University of Alabama.

William's mother was Amelia Gayle, the daughter of John Gayle, governor of Alabama from 1831 to 1835. He was a presidential elector in 1836 and in 1840 and afterwards served in Congress.

William took his collegiate degree at the University of the South in 1875 and his medical degree at Bellevue Hospital Medical College, New York City, in 1879. As a student at Bellevue he listened to the first course of lectures given by Dr.

William H. Welch, who had recently returned from his European studies and who was destined to become the father of scientific medicine in this country. General Gorgas frequently referred to Dr. Welch as his revered and beloved teacher, and it is more than probable that the lectures of Dr. Welch stimulated the spirit of research in young Gorgas, as later courses of lectures by the same distinguished man have stimulated hundreds of others at Johns Hopkins. After serving one term as an intern in Bellevue Hospital, Gorgas entered the Medical Corps of the Army. In 1881 Gorgas and Crowder were young officers at the post at Brownsville, Texas. In that year an epidemic of yellow fever prevailed at this post. An order was issued that no officer should come in unnecessary contact with a case of yellow fever. Crowder was officer of the day and on making the rounds he found Gorgas making an autopsy on a man who had died from this disease. Crowder told Gorgas to wait while he secured his sword. Gorgas continued his dissection and Crowder, properly equipped, came back to the hospital, placed Gorgas under arrest, and carried him to the calaboose. The spirit shown by Gorgas in making this autopsy continued with him throughout life and made him the greatest expert on yellow fever the world has ever known and will secure for him the honor of having eradicated this disease from many parts of the world. From their Brownsville days Crowder and Gorgas remained fast friends and during the World War there was the closest affiliation between the office of the Surgeon General and that of the Provost Marshal General. Both Gorgas and Crowder delighted in telling the story of the former's arrest by the latter at Brownsville in 1881.

In 1898 Captain Gorgas went with the Fifth Army Corps to Santiago and while there was promoted to the rank of major. In the Santiago campaign Gorgas had charge of the Yellow Fever Hospital and it was largely through his skill in the management of this disease that the death rate in our Army in Cuba from the disease was so low. In charge of the yellow fever patients at Siboney he was untiring in his efforts to limit the spread of the disease and to properly treat the sick. The sight of his kindly face was a stimulant which did much to tone up the muscles exhausted by the exercise imposed upon the body by *el vomito negro*. His kindly words to his patients served as better tonics than any named in the pharmacopeia. As one of his patients at that time the writer testifies to the kindness and skill of Gorgas from personal experience. At Siboney Gorgas contracted typhoid fever and was seriously ill for several weeks. After his recovery in the fall of 1898 he became chief sanitary officer of Havana. In this position he was in closest touch with Major Reed and his associates in their investigations concerning the transmission of yellow fever. After Reed had demonstrated the truth of the theory of Finlay and had incriminated the stegomyia, it was believed that the fight against this disease was to be waged by immunizing susceptibles by the bites of infected mosquitoes, but this did not prove practical. To Gorgas belongs the credit of having originated and executed methods for the extermination of the stegomyia. He carried this out so successfully in Havana that the city for the first time in several hundred years was free from the disease.

When the building of the Panama Canal was undertaken Colonel Gorgas was made chief sanitary officer of the Zone. It is no exaggeration to say that his work on the Zone rendered the building of the canal possible. It is estimated that

for every tie on the Panama railroad the French left a skeleton on the Zone. Gorgas so improved the sanitary condition of this death laden region that it became healthier and showed a lower death rate than any community in the United States; indeed, on the Canal Zone Gorgas demonstrated that malaria and yellow fever might be banished from the tropics and the fairest and most fruitful regions of the world might become fit and even delightful habitations for man.

After the completion of the Isthmian canal Gorgas was made Surgeon General and in his honor the rank attached to this office was raised from a brigadier to a major generalship.

It is exceedingly fortunate that during the World War General Gorgas occupied the position of Surgeon General of the Army. Everybody knew of him, was acquainted with the work he had done and had implicit confidence in him both as a skilled sanitarian and as a man of honor. During the war his chief concern was the welfare of the soldier. He personally inspected all the camps and a notification that any camp had an undue amount of sickness was sufficient to bring General Gorgas to it with the greatest speed. In making his inspections he insisted that he and those who accompanied him should take at least one midday meal in the hospital unannounced and with the purpose of ascertaining by personal experience how the patients were fed. He not only adhered to this rule himself, but insisted that all inspectors should do the same. The skill and devotion of General Gorgas to the welfare of the enlisted men resulted in the mobilization of a great army with a smaller death rate than had hitherto been known in the annals of military medicine.

General Gorgas was deeply interested in the Medical Reserve Corps and it was largely through their knowledge of his work and their faith in the man that more than thirty thousand civilian physicians immediately offered their services to him. At the beginning of the war the highest rank that a Reserve officer could secure was that of major. General Gorgas prepared with his own hands a bill providing for increased rank in the Reserve Corps and personally appeared before Congressional committees to secure the passage of this bill. In this he was successful. He was not content to visit the camps in this country, but made a tour of those in France.

General Gorgas' splendid work has received universal recognition. Before the War he was called by the British Government to South Africa to advise as to the methods necessary for the eradication of infectious pneumonia on the Rand. He was given degrees by many universities in this country and by the University of Oxford. He received many decorations, both in this country and abroad. His great ambition was to completely eradicate yellow fever and after his term as Surgeon General had expired he went to South America as a health commissioner for the International Health Board of the Rockefeller Foundation. At that time and for many years previously Guayaquil had been a hot bed and breeding-place for this disease. He succeeded in completely stamping out this disease at that place. A few months ago yellow fever was reported on the west coast of Africa and General Gorgas was asked by the British Government to visit that region and determine whether or not the reported disease was yellow fever, and if so how it could be eradicated. On his way to South Africa he was stricken with a cerebral hemorrhage in London and there died.

Certainly if service to his fellow man be a measure of greatness, General Gorgas' name will take a place with those of Pasteur, Koch, Ross, Reed, and others of this class. We mourn his death, but we recognize the fact that he built for himself, for the medical profession, and for the world at large, a monument more lasting than one of stone or bronze.

To know General Gorgas was a high privilege and an education in and of itself. He was as gentle as a woman, but at all times inflexible in his adherence to what he believed to be right. He would listen with the greatest patience and deference to any suggestion, but he always acted in accordance with the dictates of his intelligence and his heart. Companionship with him was heightened by the vein of true wit and humor which ran through much of his conversation and his writings. His book on Sanitation in Panama is interspersed with stories which would have done credit to Mark Twain.

It was his custom to begin or to end his interviews with some humorous remark. The sparkle in his eye always foretold some humorous suggestion. After a conference with the writer he once said: "This is your judgment and it is mine, but remember that your judgment and mine have at times been at fault. Do you recollect that you and I recommended the burning of the village of Siboney in 1898 in order to stamp out yellow fever? I have often wondered how many infected mosquitoes were destroyed in that conflagration."

His story of the stampede among a group of distinguished sanitarians, who while visiting the hospital in Havana and standing around a jar filled with mosquitos some one accidentally displaced the top of the jar and set free the host of winged insects, is only equaled by that of the turkey gobbler at the hospital at Ancon that became blind from swallowing the quinine capsules surreptitiously dropped in the bushes by the laborers to whom they were issued as a daily ration. We hope that Mrs. Gorgas will publish his letters. In doing so she would confer a favor and, indeed, we may say, a boon upon the medical profession. They would display the inner man of one who has done great things for the good of mankind and one we all delight to honor.

In 1885 General Gorgas married Marie Cook Doughty, of Cincinnati, who has accompanied him on many of his journeys in search of infection and has intelligently helped him in his work. They have one daughter, the wife of Colonel W. D. Wrightson, who was one of General Gorgas' chief aids on the Canal Zone, chief of the Sanitary Corps during the War, and since that time an assistant to General Gorgas in his work in Central and South America.

The Medical Corps of the Army, the medical profession of this country and of the world, all who are interested in the eradication of disease and the alleviation of human suffering, recognize the greatness of the man and his work and deeply mourn his death. May his life be an incentive to the young men in our profession.

—V. C. V.

Prevention of Goiter

WHILE it is possibly true that the majority of goiters one sees so frequently in children in grade schools, and high schools; in adolescents in colleges and offices, and in adults in the market places and department stores, wherever there are crowds, are benign, i.e., they produce no symptoms, nevertheless, they

are abnormalities which have in them vicious potentialities. If it were possible to suppress them, to keep the thyroids within bounds morphologically as well as physiologically, the community would be better off. At least the cosmetic effect would be good, and also possibly the morbidity rate would be reduced in certain directions. Just how far the latter would be true cannot be estimated as yet, but in the course of years a valuable statistical material will have gathered in the city where Marine has commenced his experiment. There are many apparently harmless conditions (and an abnormally enlarged thyroid may be one of them), which are expressions of variations in structure and metabolism which tend in the direction of diseased conditions, the connections of which are not at present understood. These directions and connections may be learned in the future by following and studying the vital statistics of districts in which the attempt is made to reduce the incidence of abnormality. In goiter districts such studies should have much value with reference to the prevalence of thyroid states, and may also point out other states and relationships of which we do not know.

It is not frequent that a physiologic experiment on a large scale is made in the community, at least it is not frequent that such an experiment is planned and carried out for a specific purpose. Such a one Marine and his co-workers have made. After years of study and experiment on thyroid states, Marine devised a scientific experiment upon a community, and in successive years has checked up the results and published them for the benefit of other communities in which the incidence of thyroid enlargement is high. The result is a valuable contribution to preventive medicine.

In his most recent report Marine gives the records of 2305 pupils in the public schools who have not taken the prophylactic treatment, and 2190 pupils who have. Of the 1182 pupils with thyroid enlargement at the first examination and who took the prophylactic, 773 thyroids have decreased in size, while of 1048 pupils with thyroid enlargement at the first examination and who did not take the prophylactic, 145 thyroids have decreased in size. The only presumptive error in these figures is due to the fact that many pupils listed as not taking the prophylactic have taken iodine in one or another form outside the school jurisdiction. The figures are striking.

The treatment used by Marine consists in administering 2 grams of sodium iodide, given in 0.2-gram doses daily for ten consecutive school days, repeated each spring and autumn. An ounce of syrup of the iodide of iron or hydriodic acid given over a period of two or three weeks and repeated twice yearly might be as efficacious. The sodium iodide treatment Marine believes has prevented enlargement of the thyroid in more than 99 per cent of the children in his district.

In the practical application of the preventive treatment, Marine and Kimball say, one must keep in mind the three periods when simple thyroid enlargements most commonly occur, i. e., (1) fetal, (2) adolescent, and (3) pregnancy. Prevention of goiter in mother and fetus is as simple as that occurring during adolescence and probably smaller amounts of iodine could be used, for instance, 1 gram of sodium iodide distributed over a month. At this period the problem is one for physicians alone. The problem during the second period is, however, a public health problem for state, county, and municipal boards of health. The ex-

isting system of organization of schools, public and private, is sufficient to handle the details without aid or expense. Physicians in industrial medicine can render important service by practical and educational methods. It seems that the maximum of prevention with a minimum of effort would be obtained by giving the treatment between the ages of eleven and seventeen years.

So far no untoward effects have been observed as a result of the treatment. No obvious case of exophthalmic goiter has developed, although such cases have been carefully watched for. Less than 0.5 per cent of the cases have shown symptoms of iodism, practically all of them mild.

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—*P. G. W.*

Significant Phenomena of Influenza Pandemics

WITH the development of greater refinements of investigation many novel features of pandemic influenza have been recognized. Many of them apparently corroborate existing theories of epidemiology while others call for further explanation or different interpretation.

Before the days of bacteriology the contagiousness of the disease was little discussed. Its infectiousness was, in fact, not universally established until the epidemic of 1889-90. Watson recorded "instances * * * too numerous to be attributed to mere chance in which the complaint has first broken out in those particular houses of a town at which travellers have arrived from infected places."[1] Parkes[2] commented on the frequency with which first cases had been introduced or imported and also how often the townspeople nearest the invalids had been infected. Leichtenstern recorded many such isolated examples.[3] Some of the earlier observers, especially Haygarth in 1775 and 1782, Falconer in 1802 and Baker in 1814, collected so many instances in support of this that they became convinced that its propagation was due entirely to human intercourse.[4]

In the literature of the period there were many examples reported from personal experience to show that influenza is transmittted from man to man. Two objections had to be met, however, before this view was generally accepted. It had been claimed by some that the disease spread more rapidly than individuals could travel and again that instances were on record of cases occurring spontaneously in isolated communities. Abbott records an example of the latter.[5]

"An impression having gained some credence that influenza had appeared on board the squadron of naval vessels which sailed from Boston in December, 1889, while on their course across the Atlantic and before their arrival in Europe, a letter was addressed by the writer to the Bureau of Medicine and Surgery of the United States Navy for information upon this point to which a reply was received, as follows:

" 'The "Chicago," "Boston," "Atlanta" and Yorktown" left Boston December 7, 1889, for Lisbon, Portugal. The first three arrived at Lisbon on December 21

without having touched at any port *en route.* The "Yorktown" arrived at that port December 23, having stopped about twenty-four hours at Fayal, Azores. * * * Influenza first appeared on the "Chicago" December 23, on the "Boston" December 28, on the "Atlanta" December 30, and on the "Yorktown" December 28.'

"Influenza was prevailing in Lisbon at the date of arrival of the squadron."

Many similar reports of epidemics on ships at sea and in other isolated communities have, in the same way, been shown to be distortions of the actual facts.

Other facts which have aided in establishing the contagiousness of influenza have been the frequent "immunity" of remotely isolated groups or of segregated individuals, such as lighthouse-keepers and inmates of quarantined institutions, as well as the tendency of outbreaks to follow the gathering of crowded public assemblages.[5]

Another argument formerly raised against the contagious character was the claim that it broke out in mass attacks—that large numbers became ill on the same day, without the occurrence of isolated antecedent cases. The first cases of such epidemic diseases as the plague became a matter of record because of the accompanying high mortality, while in influenza with its relatively low mortality, the record usually begins only after a comparatively large mass of individuals has been attacked. Detailed studies of the Munich epidemic of 1889,[6] and numerous similar studies of the recent epidemics have shown a period of two or three weeks of steadily increasing numbers of cases before the height of the epidemic was reached.

The Epidemic of 1889-90 was first recognized as such in October, 1889, when it appeared in Northern Russia. It first occurred in St. Petersburg in the last week of October. In the following month cases appeared in Paris, Vienna, and Berlin, and it did not reach London until December. South America was reached in January, 1890. This does not indicate more rapid progress than the rate of human travel of that period. The period of greatest mortality at Stockholm followed that at St. Petersburg by three weeks, that of Berlin, by yet another week. This period for Paris was a week later than for Berlin, that for London another week later, and that for Dublin three weeks later than that for London. The week of highest mortality in Dublin was later than that for New York or Boston.

The earlier epidemics progressed even more slowly. That of 1762 prevailed in Germany in February, in London in April, in France in July and in America in October. Epidemics have varied not only in rapidity of spread but also in extent of spread. Of the 72 epidemics on record since the thirteenth century, thirteen have spread to nearly all inhabited parts of the earth. Between 1847 and 1889 there was no pandemic, but the disease had prevailed in more or less-limited areas, as at Paris and Strassburg in 1857-58 and in 1867. This appears to have been true for all periods.

It has been more difficult to trace the site of origin of the last epidemic and its direction of spread. Several factors have contributed to this, the principal of which are the speed of modern travel, the character of modern commerce, and the existence of war. The channels of the commerce of today radiate

nearly from all points to all other points of the civilized world. An epidemic breaking out in Turkestan or Sweden could be carried as directly and nearly as rapidly to New York or Singapore as to Naples, Lisbon or Liverpool. No longer are there a few preeminent lanes of travel such as there were in 1580, when the epidemic spread clearly from Constantinople to Venice and on to Hungary and Germany, finally finding its way to Norway, Sweden, Denmark and Russia. The war has made it difficult to know accurately the date and direction of spread in enemy countries. The broad dissemination of trade with belligerent countries adds to the difficulties of following routes of travel and of spread.

The autumn epidemic has been reported as being at its height in October, 1918, in such widely separated localities as the United States, England, France, Brazil, Greece, India, Japan and Korea. There was no such rapid wide dissemination as this in previous epidemics. It may be a question whether the spring of 1918 with its much milder epidemic was not the actual period of spread from an endemic focus to all parts, and whether the autumn epidemics consisted in recrudescences of the disease already planted in these localities. This point will be discussed later.

Influenza was recognized in the United States Army in this country in March and April of 1918.[7-8] There is also good evidence that the civilian population was attacked at the same time in certain localities. The first outbreak in the American Expeditionary Forces is recorded as in April and May, 1918, the first cases being near a port of debarkation. The second epidemic occurred in September and October and the third recrudescence in February, 1919.[9] In Greece the disease first appeared toward the end of May, 1918. The severe form appeared in September.[10] A mild epidemic passed through Spain in the early spring of 1918, then visited France and probably extended into Germany. It was mild in the two former countries. By July it had become relatively severe in Germany.[11] In England an epidemic was prevalent in June and July[12] and in Scotland in July and August.[13] A mild epidemic occurred in certain parts of Britain in May. Recurrence occurred in October and November, 1918, and in February and March, 1919.[4-10] Japan was afflicted with the mild form of the disease in the spring of 1918 and it had invaded India by August.

Thus we see that a mild and rather less highly contagious form of the disease had planted its seed in nearly all countries during the spring and early summer. Since then we have had a severe recurrence in 1918, a less severe one in 1919, and yet another in 1920.

The tendency to recurrence is characteristic of epidemic influenza. Can we go farther and state that the curves of incidence tend to vary in any set fashion with the successive recurrences? Greenwood[12] describes the salient features of the primary epidemic as, first, a rapid and quasi-symmetrical evolution, and, second, a frequency very closely concentrated around the maximum. In other words the duration is short, the rise to a peak rapid and the subsequent fall equally rapid. He shows that in the July-August, 1918, epidemic in Great Britain nearly 80 per cent of the total incidence in the localities studied was grouped within three weeks time. This was also true for the primary attack of 1889. In contradistinction a secondary epidemic affects, according to Green-

wood, a relatively small proportion of the population, is slower in reaching its maximum, and thereafter declines slowly and irregularly, more slowly than it increases. The distribution of the curve is less symmetrical and there is less concentration around the maximum. A secondary epidemic is characterized by a much higher fatality than a primary one.

In England from 1889-94 there were four epidemics. The first was primary in character, the second secondary, and the third, while reverting to primary type in respect to symmetry remained of the secondary type as regards mortality. The epidemic of 1676 appears to have caused more deaths than the primary one of 1675. That of 1679 reverted to the primary type. One hundred years later, in 1782, a summer epidemic occurred in London, followed the next year by another which appears to have been of about equal severity. The pandemic of 1847-48 appears on the contrary to have been a single primary epidemic without recurrence.

If we accept Greenwood's classification we must conclude that the autumn of 1918 epidemic in this country partook of the nature of a primary epidemic in most localities as regards symmetry and explosiveness, but affected a much larger number of people and was much more highly fatal than the spring epidemic. That of 1920 was equally explosive, but less severe. The epidemic in Detroit illustrates the manner of the last recurrence.[14] On the 27th day of the 1920 epidemic the death rate had returned nearly to normal and the epidemic had run its course. There had been 11,202 cases with 1,642 deaths. On the 27th day of the 1918 epidemic there had been 16,423 cases, 1286 deaths, and the epidemic had not run its course. The second outbreak was of shorter duration and affected a smaller number of the population, but had been more highly fatal.

Greenwood alludes to the fact that the epidemic constitution of a secondary influenza period is pneumonic, as contrasted with a primary period which is usually without serious complications. This was true in England, in America, in Europe, as exemplified by the experience in the American Expeditionary Forces. There the spring epidemic was so mild as to be designated by the descriptive title "three day fever." If the secondary epidemic should occur in the winter it might well be most severe, while in the summer it could be very mild.

Is there any tendency to regularity in the interepidemic intervals? Brownlee[15] after studying the records of 1889-94 and the intervening years concluded that for some reason influenza periods tend to recur at thirty-three week intervals after the primary epidemic, and that the favorable season for its occurrence is from January to the end of May. Should the thirty-third week fall in other than these winter months the epidemic may be mild or even missed, reappearing after another eight months' interval. Epidemic influenza does not assume a form which causes any large number of deaths until a bronchitic or pneumonic constitution has been established. The fatal form is usually a disease of the winter or spring.

Reasoning thus, Brownlee was able to predict correctly the date of the recent 1920 epidemic. He did not attempt, however, to explain the short interval between the two epidemics of 1918. He speaks of the second as "aberrant." In other words it does not fall within his classification. October is not a high respiratory disease month. The epidemic should have been mild.

Stallybrass[16]; has confirmed Brownlee's thirty-three week periodicity and suggests an explanation for the aberrant October epidemic. Using periodograms with a thirty-three week basis, and plotting deaths from influenza and respiratory diseases from January, 1890, through January, 1920, he finds that the most definite thirty-three week periodicity is shown during the years 1890-99. During this period there is one maximum, when all thirty-three week periods are superimposed, which occurs at the seventh week of the cycle. Beginning about 1899 a new maximum appears in the nineteenth week of the cycle, which continues to recur until the culminating point is reached in the week ending October 26, 1918. An additional sixty-six weeks carries the date forward to the first week in February, 1920. The maximum at the seventh week of the periodogram during the years 1899-1913 is greatly diminished from that in 1890-98. The periodogram for 1914-1919 shows clearly both maxima, that in the seventh and that in the nineteenth weeks. The interval 1914-1919 was chosen for separate tabulation because from 1914 onward there was a progressive increase in the annual number of influenza deaths, with the single exception of 1917.

There is still a third small but definite maximum in both the early and late periodograms, at the twenty-seventh to the twenty-ninth week. The twenty-ninth week of the cycle falls on May 18, 1918, and on January 10, 1919. Crests of influenza deaths actually occurred in Liverpool on May 18, 1918, and January 3, 1919. There were also outbreaks in the Grand Fleet, in Spain, Glasgow, and other places in May, 1918.

Stallybrass bases his figures chiefly on death rates in Liverpool, Brownlee, on those of London.

It becomes apparent that there are probably three sets of phenomena, each with thirty-three-week cycles, the first reaching its crests in May, 1918, and January, 1919, the second in October 1918, and, after sixty-six weeks, February, 1920, and the third in July, 1918, and March, 1919. Crests of influenza waves occurred in all of these months, at one place or another and sometimes all in the same locality. These observations go one step farther toward explaining the "aberrant" October epidemic. This particular outbreak falls about the nineteenth week and, therefore, is in the cycle which has become increasingly prominent since 1900.

Stallybrass remarks, "if it should prove correct that there are three strains of the influenza virus, each with a periodicity of about thirty-three weeks, and that simultaneously all three strains became enhanced in both virulence and infectivity, then we are faced with a phenomenon without exact parallel, although the behavior of the meningococcal viruses during the war present some points of similarity."

In addition to the thirty-three-week cycle, there is evidence of a larger, basic cycle of about ten years' range. Epidemic crests have been reached in England in 1789-90, 1802-03, 1830-32, 1840-41, 1848-51, 1854, 1869-70, 1879, 1890, 1898, and 1918-20.

Are the sporadic interepidemic cases encountered by the practitioner of medicine and diagnosed as influenza, the same disease as that which we have been discussing? Are they due to the same cause? This is a vital question in the epidemiology of the disease. Some have taught that there is somewhere far away,

perhaps in Turkestan, an epidemic focus where the disease smoulders for years occasionally flaring up and covering the earth with its conflagration. It has even been suggested that we search out this "foyer" and by appropriate procedures in that locality, eradicate the disease forever.

But if the disease is constantly with us in milder form, its eradication would not be so easy a matter. No disease is more characteristic, or conforms more nearly to type than does epidemic influenza. The symptoms are clear cut, the manner of spread is constant, and the epidemic as a whole has the definite features previously described. The sporadic case has the same quite clear-cut clinical symptomatology, but fails to manifest the one feature most characteristic of epidemic influenza—a high degree of contagiousness. Further, although the symptoms in themselves are characteristic, there is no one pathognomonic sign by which one may say "this is a case of influenza," and, finally, other disease conditions frequently resemble it so much as to cause error in diagnosis.

Thus, while probably not all sporadic cases diagnosed influenza are in reality that disease, yet there have been plenty of instances thoroughly studied by the best clinicians, where no other diagnosis could be accepted. Such observations as those of Brownlee and Stallybrass also indicate that the disease is always with us in mild form. Then there is the added significance of local outbreaks, limited to an institution or a town or a small section of country, but not becoming pandemic. These do not trace their origin to Turkestan. Examples are numerous. Outbreaks in Paris and Strassburg in 1857 and 1867 have already been referred to.

An excellent example of an epidemic limited to an institution was described in 1869 by Webster.[17] The number of inmates was about five hundred, of whom one-fourth were attacked, and a large part of these applied for treatment. These cases usually presented the following symptoms: *Prostration*, often so great as to require patients to take to their beds. *Chills* with great sensibility to cold. *Headaches* and frequently *vertigo*. *Fever* apparently higher than that which is common in the early stages of typhoid. *Insomnia, anorexia* and *thirst*. Cough and expectoration in all cases. No physical signs were detected in the lungs where they had been previously healthy. The acute stage ran its course in from three to five days, and subsided gradually, leaving the patient weak and with an obstinate cough, which did not yield for weeks or months. Not every case presented all these symptoms. There was every degree from very severe to light cases. They agreed in one characteristic, that the constitutional disturbance was primary and was out of proportion to the local catarrhal lesion. The epidemic ran its course in about a month, the epidemic influence growing weaker, the severer cases occuring in the first weeks of the epidemic. There were no fatal cases. There were a few cases of pneumonia and pleurisy, and in every case of phthisis the rational symptoms and the physical signs were greatly aggravated for a time. There had been no cases, either of pneumonia or of pleurisy prior to this epidemic. There was at the same time a prevalence of "colds" in the neighboring city of Augusta, Maine, but they lacked the severe constitutional symptoms which prevailed at the asylum.

There was no pandemic of influenza at the time of this outbreak, but there are records of local epidemics in England in 1869.

Assuming that a disease similar to influenza is present in greater or less degree during interepidemic periods, can the virus infecting these mild cases become the cause of the fearful pandemics, or must we still have recourse to Turkestan?

The answer to this question lies in the future. We have quoted Brownlee and Stallybrass as giving evidence of its constant presence. It will be objected that their figures are for all respiratory infections, that in interepidemic periods pneumonia and bronchitis may alone make the total numbers. While this is true, the fact remains that there is a close correlation between the waves of the periodogram and the actual dates of the recent recurrences. Perhaps it would be more correct to say that the respiratory infections, including influenza tend to recrudesce in thirty-three-week cycles.

The periodogram as used by Brownlee and Stallybrass is not without possible error. The including of the large 1918 wave so overshadows all previous waves as to distort the entire picture.

We are presented with a variety of facts concerning the origin and manner of spread of pandemic influenza,—facts many of which seem directly contradictory. What information we possess of former pandemics indicates geographic progression from an initial focus. Description of the site and size of this focus is usually vague. Evidence presented within the last year or two, on the contrary, emphasizes the constant presence in many localities of an infectious phenomenon whose salient characteristics are a tendency to periodicity and occasional outbreaks of respiratory pandemics with no break in the periodic cycle. Finally, and to further complicate the picture, we know that during the severe 1918 epidemic there was geographic progression. Pandemic influenza entered the United States in August and September, 1918, at Boston and Camp Devens and spread thence, south and west, to cover the entire country.[18] It entered Connecticut at New London and appears to have spread from there, northwest and west, spreading more rapidly along the more highly-travelled routes.[19] The spread from Spain across France and Germany has been described.

In 1918, the epidemic very evidently spread across the United States from city to city, from east to west. In 1920 this spread was not so evident. The disease was first reflected in the total mortality in Kansas City during the week ending January 17, 1920. The following week increase was recorded in Chicago, New York and Milwaukee, and still a week later in Detroit, Boston, San Francisco and Philadelphia. The mortality increase in New Orleans did not commence until the week ending February 14th.[20] The earlier cases appear to have been in the central area of the continent, and quite unrelated to still earlier epidemics reported in Europe, particularly in Spain.

Certainly pandemic influenza is a contagious disease spread by personal contact, capable of traversing entire continents in remarkably short time, but spreading no faster than the present means of human travel. Surely also the spread is from some focus. But the question, that recent epidemiologic work has raised is whether we must still assume one far off endemic focus, or whether the primary focus may occur wherever and whenever all conditions, biologic, telluric, meteorologic, become propitious to an increase in virulence of the disease virus?

If the latter be true, there might conceivably be two or more simultaneous primary foci, or, if there be more than one virus, each with its own periodicity, more than one epidemic might manifest itself in the same focus or locality.

Such a conception is not entirely new. Leichtenstern[21] in 1896 suggested the possibility of two endemic foci, one in Eastern Europe or Asia and the other in North America. He also considered the secondary epidemics as arising from many foci, left after the spread of the primary waves.

The mechanism which produces an increased virulence may be more easily understood from a consideration of the following remarks by Theobald Smith.[22]

"During the elimination of the more virulent races of microorganisms, there goes on as well a gradual weeding out of the most susceptible hosts. In a state of nature in which medical science plays no part, there must occur a slight rise in the resistance of individuals, due to selection and perhaps acquired immunity, which meets the decline of virulence on the part of microbes until a certain norm or equilibrium between the two has been established. This equilibrium is different for every different species of microorganism, and is disturbed by any changes affecting the condition of the host or the means of transmission of the parasite. One result of the operation of this law is the low mortality of endemic as compared with epidemic diseases. Certain animal diseases while confined to the enzootic territory, cause only occasional, sporadic disease, but as soon as they are carried beyond this territory, epizootics of high mortality may result. Climate in some cases enters as an important factor, but the most important, perhaps, is the *slight elevation in virulence brought about by a more highly resistant host.* The most susceptible animals are weeded out, and the rest strengthened by nonfatal attacks. *The virulence of the microbe rises slightly to maintain the equilibrium.* In passing to a hitherto unmolested territory, the disease rises to the level of an epizootic until an equilibrium has been established.

"In the more or less rapid changes in our environment due to industrial and social movements the natural equilibrium between host and parasite established for a given climate, locality, and race or nationality is often seriously disturbed and epidemics of hitherto sporadic diseases result."

An example of increasing virulence from such changing conditions, is the experience in the army camps with the streptococcus. This microorganism became so exhalted that, whereas, it was at first but a secondary invader, it soon became the cause of primary disease.

With our present knowledge the assumption of widespread endemic influenza with multiple primary foci and any attempted explanation thereof must be but mere conjecture.

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—*W. T. V.*

The Rationale of Narcotic and Antipyretic Therapy

THE therapeutist of today may look back with tolerant amusement on those ancient pioneers who, believing in the doctrine of signature, were wont to prescribe liverwort for disease of the liver and milk weed as a galactagogue. These early followers of the art believed that from the shape or color of a leaf, a root, a blossom, from a superficial resemblance to some organ of the human anatomy, they might divine what malady the Creator had intended be cured thereby. In those days there were nearly as many remedies from which to choose as there were varieties of plants. Many of them used quite empirically were found to be highly beneficial. Today the drugs of proven value scarcely number half a hundred.

The physiologic action of most of the members of the latter group is now well known. A few of proven worth are still accepted as valuable empirical remedies. Pharmacologic knowledge has been gained chiefly through laboratory experiments on animals; to a lesser extent through observations of the effect on disease in man. Quite unconsciously we are still using some drugs whose physiologic action is well known, entirely empirically so far as concerns their manner of action on the particular symptom to be relieved.

Thus one may dissertate at great length on the action of morphine as a myotic and concerning its action in slowing the respiration or lessening peristalsis. But we do not give morphine to contract the pupils or to slow the respiration. We administer it empirically to relieve pain, and that it accomplishes better than any other drug. Here we are not dealing with its ability to alter the function of a particular organ so much as with its action on psychic processes.

D. I. Macht and his co-workers have in recent years studied this problem, which they designate "psychopharmacology," and Macht has recently published (Bull. Johns Hopkins Hosp., May, 1920) a summary of their results.

They first studied quantitatively the extent of analgesia produced by the various opium alkaloids. They determined the sensory threshold value for pain by electrical stimulation on various parts of the skin and mucous membranes before and after the administration of the drugs. Martin and others had previously determined that the threshold of electrocutaneous sensation is quite constant in normal individuals and is subject to physiological, diurnal, nocturnal and fatigue variations. The present investigators found a normal pain threshold which remained constant for many hours in succession and with but slight diurnal and nocturnal variations.

They then administered the drug to be examined either subcutaneously or intramuscularly, the subject being ignorant of the nature of the drug. These experiments were conducted under constant conditions and were suitably controlled. They concluded that the narcotic drugs administered in moderate therapeutic doses fell in the following order with respect to their analgesic power, beginning with the strongest: morphine (10 mgs.), papaverin (40 mgs.), codeine (20 mgs.), narcotin (30 mgs.), narcein (10 mgs.), and thebain (10 mgs.). In one subject with morphine idiosyncrasy they discovered that small doses rendered him hypersensitive to pain. This confirms the common experience of persons who are not relieved by morphine but are thereby rendered more sensitive.

They further found that certain combinations produced greater analgesia than either drug given separately. Thus, narcopthin, (morphine and narcotin meconates), produced distinct analgesia in 5 mg. doses, while 5 mg. of morphine or 10 mg. of narcotin alone failed to produce this effect.

Attention was next directed to the local or peripheral action of the opium alkaloids, a subject concerning which there has been considerable difference of opinion. Dionin or ethyl morphine is well known to be a powerful local anesthetic and is used as such in ophthalmic surgery. Monkhtar demonstrated a local action on sensory nerve terminals. Pal discovered accidentally that papaverin placed on the tongue produces numbness. Macht and his associates found that the opinum alkaloids, when applied to the skin or the mucous membranes, affected the sensory nerve endings with a resultant raising of the threshold for pain. The most efficient was papaverin. Narcotin, morphin, narcein, codein and thebain followed in the order of efficiency. They also found that analogous to the results after subcutaneous injection pantopon, (a mixture of the total opium alkaloids), exerted an affect greater than that produced by the same amount of either morphine or papaverin.

Thus we see that opium acts both as a poison on the central nervous system and to some extent on the peripheral nerves. The old empirical local application of opiates to relieve pain appears to have a rational basis.

The common antipyretics when studied in the same manner as the opium derivates were also found to produce a certain degree of analgesia of central origin, but of lesser degree than the latter. Acetanilid, acetphenetidin and pyramidon were found to be especially effective in this group. They were administered by mouth.

In an investigation of the effects of opium derivates on psychologic reaction time, the simple reaction to touch, light and sound stimulation was tested first under normal conditions and second after injection of a drug. All experiments

were carefully controlled. Complex reaction time or associated reaction time was also determined by having the subject add given numbers, etc. In this manner the action of the opium alkaloids on the higher brain centers was studied.

Small doses of morphine (4-6 mg.) produced a primary stimulation with shortening of the simple reaction time and a lesser number of errors made in the computation of mathematical problems. This primary effect was followed in a half hour or more by a stage of depression with prolongation of the reaction time. With doses of 8-15 mg. of morphine the stage of stimulation was very short and the depression became the dominant feature, with delayed reaction time and a greater number of mistakes in the association tests.

In four out of seven experiments with pantopon, a mixture of the hydrochlorides of all the opium alkaloids, and containing 50 per cent of morphine, the narcosis and prolongation of the reaction time was greater than that produced by an equal amount of morphine.

With very small doses of morphine, only the primary stage was observed.

In all experiments the simple reactions were less affected than the association tests, indicating an action especially on the higher functions of the brain.

The effect of the antipyretics on the reaction times was quite different. There was no primary stimulation effect, except possibly after small doses of quinine, and in ordinary doses these drugs produced little effect on the reaction time, tending if anything to delay it slightly. Such depression was noticed particularly in the case of pyramidon. This corresponds to the common experience that it is a more powerful analgesic than the other antipyretics. It is interesting that when there was a depressant effect it was more marked in the simple reactions to light, sound and especially touch than on the higher association processes, although there was some impairment of the latter. Thus, the absolute readings in case of the mathematical calculations were sometimes actually improved, the depressant effect being seen only in the greater number of errors committed. These reactions were the reverse of those found for the opiates and suggest some lower synapse as the seat of action of the coal tar derivates.

In the neuromuscular test of continuous tapping with a brass stylus it was found that less than 5 grains of phenacetin, antipyrin, acetanilid and quinine showed a tendency to improve the tapping rate, while doses of 8 or more grains tended to impair the efficiency in the test. Pyramidon, salol and aspirin had no appreciable effect.

Morphine and pantopon injected subcutaneously produce a definite narrowing of the field of vision, whereas the antipyretics tend if anything to increase it slightly. It is difficult to establish the mechanism of these phenomena. Macht suggests that constriction of the pupil in the case of opium, vasomotor changes produced by the antipyretics, specific effects upon the retinal ganglia and nerves, and the central cerebral effects must all be considered.

The acuity of hearing was increased by antipyrin, pyramidon and quinin and decreased by acetanilid, salol and aspirin. A remarkable synergistic action was seen in some drugs as in acetanilid and sodium bicarbonate. Taken alone, the former decreases the acuity of hearing while the latter has no effect whatever. The two taken together produce a definite improvement in auditory perception.

Morphine administered to albino rats who had previously learned to negotiate an experimental labyrinth produced a marked impairment of the memory habit and activity. But even after a prolonged narcotization the animals ultimately recovered all of their "intellectual" activities. Macht suggests that this is hopeful evidence for ultimate recovery in the cure of drug addicts. While we welcome all such evidence we must bear in mind that the psychologic reaction is much more complex in humans than in rats, or at least than the recognizable reactions in these animals.

—*W. T. V.*

The End Results in Cases of Focal Infections

CONSIDERING the enthusiasm which attaches to focal infection, it is perhaps no wonder that many almost crimes are committed in its name. Has a patient an ache or a pain? He must have a diseased tonsil or a carious tooth, or a root abscess, or an infected sinus. So, it will be easier to take out the tonsils and make the diagnosis later, or take out the teeth or drain a sinus, and, if the symptoms cease, all well and good; if they do not, well, let's look farther. Focal infection has become an excuse for snap-shot diagnosis. It occupies, in some quarters, the same position as does the exploratory laparotomy. It deserves to be said very emphatically that the state of affairs pictured above is not a general one, albeit too general. Rather it is itself a sort of focal infection that truly causes aches and pains in the body medical. The treatment is obvious.

The contrary state of affairs also exists. There are physicians who decry the emphasis,—any emphasis, indeed— upon focal infections. Such an attitude is probably a more serious one than that of the positive enthusiast, for after all a man is not damaged save only temporarily by the loss of his teeth or tonsils.

Between these two extremes of absolute faith and clinical agnosticism lies a mean. How much truth and how much poetry is there in the whole situation?

Fontaine* has taken 100 cases, and discusses them from the standpoint of the end results. In each case the relation of the focus of infection to the symptoms in question has depended upon: (1) the absence of any other demonstrable cause for the symptom; (2) the failure to cure the symptom by all other methods than the one used, and (3) prompt and continued relief, with no return of the symptom, on the cure or eradication of the focus of infection. Be it said in passing that Fontaine evidently studied his cases and that the conclusions were arrived at largely through the cooperation of a group of specialists. Great reliance was placed on roentgenograms.

In this series the teeth were the most common source of infection, and all sorts of dental conditions were included. Most common, however, were either apical abscesses or granulomas at the roots of devitalized teeth. Next in order of importance were tonsils, and in this group the small fibrous, or submerged, tonsils were quite as frequently involved as the visible sort. The sinuses were of least importance.

The most frequent symptom was pain, for which relief was sought in 42 per cent of the cases, and it occurred, usually, in the muscles of the neck, back,

*Fontaine: Jour. Am. Med. Assn., 1920, lxxiv, 1629.

chest or limbs. The painful areas were not affected by changes of temperature nor were they often associated with tenderness. These symptoms were most frequently associated with dental lesions.

Fever was the symptom second in importance to pain, and was present in 18 per cent of the cases. It seldom exceeded 101° F., was not often accompanied by chills, and in a few cases was accompanied by night sweats. Such cases suggested incipient tuberculosis. In them the foci were equally distributed between the teeth and the tonsils.

Chronic headaches was the dominating symptom in 4 per cent of the cases, and in each case the focus was tonsillar.

General debility with loss of weight and strength occurred in about 10 per cent of the cases. This syndrome was, as a rule, observed in middle aged adults, and in most cases it was accompanied by obvious disease of the teeth.

Severe secondary anemia occurred in 4 per cent, and these cases were due in equal numbers to disease of tonsils or teeth.

There were 6 cases of albuminuria, four due to tonsillar foci, two to dental.

Six cases had an achylia gastrica. In all the only focal infection was in the mouth.

In 6 per cent of the cases moderate vascular hypertension (Systolic = 150 – 170) occurred. All of the patients were middle aged; most of them women. In all the focal infection was dental.

No acute joint conditions were reported. There were eight cases of chronic arthritis of the deforming type. None was benefited by attacks upon foci of infection in teeth, tonsils or sinuses.

In other words in the groups in which general debility, achylia gastrica, and hypertension were dominant, representing some 22 per cent of the cases, the teeth alone were at fault. In the headache group the tonsils alone were diseased. When pain was present, the foci were usually in the teeth. Fever and anemia were due equally to dental and tonsillar conditions, and in albuminuria the tonsils dominated the situation.

The whole report serves, it seems, to emphasize the importance of hidden foci, i. e., foci of infection that are drained only by the blood stream. Lesions that have free access to the exterior are much less apt to be associated with metastatic infection. Hence it is that root abscesses are so much more frequently productive of harm than the usual tonsillar infections.

—*P. G. W.*